

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
10 May 2002 (10.05.2002)

PCT

(10) International Publication Number
WO 02/37209 A2

(51) International Patent Classification⁷: **G06F**

Shantanu, V. [IN/US]; 3343 Ariel Joshua Court, San Jose, CA 95135 (US). JEVONS, Luis [US/US]; 701 Ramona Avenue, Sunnyvale, CA 95135 (US).

(21) International Application Number: PCT/US01/26390

(74) Agent: ZITKOVSKY, Ivan, D.; 6 Freeman Circle, Lexington, MA 02421-7713 (US).

(22) International Filing Date: 22 August 2001 (22.08.2001)

(81) Designated States (*national*): CA, JP, US.

(25) Filing Language: English

(84) Designated States (*regional*): European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR).

(26) Publication Language: English

Published:

(30) Priority Data:

60/226,999 22 August 2000 (22.08.2000) US
60/286,578 26 April 2001 (26.04.2001) US

— without international search report and to be republished upon receipt of that report

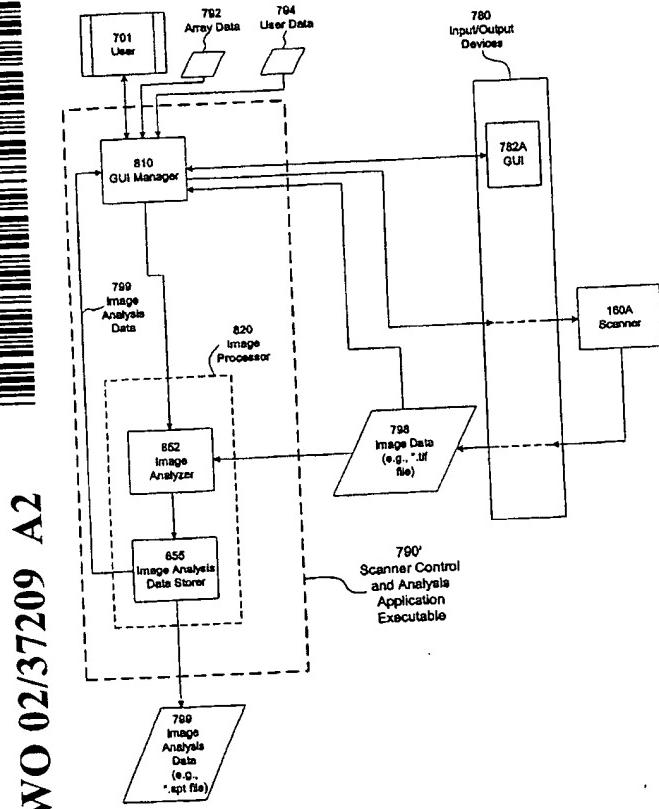
(71) Applicant (for all designated States except US):
AFFYMETRIX, INC [US/US]; 3380 Central Expressway, Santa Clara, CA 95051 (US).

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(72) Inventors; and

(75) Inventors/Applicants (for US only): KAUSHIKKAR,

(54) Title: SYSTEM, METHOD, AND COMPUTER SOFTWARE PRODUCT FOR LINKED WINDOW INTERFACES



(57) Abstract: Systems, methods, and computer program products are described for providing a graphical user interface (GUI) that may include a first openable window of image features constituting, for example, a pseudo-image of a scanned probe array. The image features each have one or more characteristics representing one or more hybridization reactions associated with a probe of the probe array. The GUI also has a second openable window including data features, each relating to one or more quantifications of one or more hybridization reactions associated with a probe of the probe array. This second window may be, for example, a scatter plot of hybridization intensities of probes to two or more labeled samples. The GUI further includes a third openable window including descriptive features such as rows of a spreadsheet. Each row may include descriptive elements associated with a probe. When a user selects a feature from any of the two or more windows, a corresponding feature in at least one other of the two or more windows is highlighted.

WO 02/37209 A2

BEST AVAILABLE COPY

SYSTEM, METHOD, AND COMPUTER SOFTWARE PRODUCT FOR LINKED WINDOW INTERFACES

5

RELATED APPLICATIONS

The present application relates to and claims priority from U.S. Provisional Patent Application Serial No. 60/226,999, titled "System, Method, and Product for Linked Window Interface," filed August 22, 2000; and U.S. Provisional Patent Application Serial No. 60/286,578, titled "System, Method, and Product for Scanning 10 of Biological Materials," filed April 26, 2001, both which are hereby incorporated herein by reference in their entireties for all purposes.

BACKGROUND OF THE INVENTION

Field of the Invention:

15 The present invention relates to computer systems, methods, and products for analyzing and displaying scanned images of high-density arrays of biological materials.

Related Art:

Synthesized probe arrays, such as Affymetrix® GeneChip® arrays, 20 have been used to generate unprecedented amounts of information about biological systems. For example, a commercially available GeneChip® array set from Affymetrix, Inc. of Santa Clara, California, is capable of monitoring the expression levels of approximately 6,500 murine genes and expressed sequence tags (EST's). Experimenters can quickly design follow-on experiments with respect to genes, 25 EST's, or other biological materials of interest by, for example, producing in their own laboratories microscope slides containing dense arrays of probes using the Affymetrix® 417™ Arrayer or other spotting devices.

Analysis of data from experiments with synthesized and/or spotted probe arrays may lead to the development of new drugs and new diagnostic tools. In some 30 conventional applications, this analysis begins with the capture of fluorescent signals indicating hybridization of labeled target samples with probes on synthesized or spotted probe arrays. The devices used to capture these signals often are referred to as scanners, an example of which is the Affymetrix® 428™ Scanner from Affymetrix.

There is a great demand in the art for methods for organizing, accessing, analyzing, and displaying the vast amount of information collected by scanning microarrays. Computer-based systems and methods have been developed to assist a user to obtain and visualize the vast amounts of information generated by the 5 scanners. These commercial and academic software applications typically provide such information as intensities of hybridization reactions or comparisons of hybridization reactions. This information may be displayed to a user in graphical form.

SUMMARY OF THE INVENTION

10 The present invention includes a system, a method, and a computer program product for controlling an optical scanner. Systems, methods, and computer program products are described with respect to some embodiments for providing a graphical user interface (GUI). The GUI may include a first openable window of image features constituting, for example, a pseudo-image of a scanned probe array. The term 15 "pseudo-image" is used in this context to mean that the image features provide a graphical representation of the probes of a probe array that typically are based on emissions from probe-target pairs, lack of emissions from probes that have not hybridized with targets, and information about the location of the probes on the probe array. The word "openable" is used in this context to mean that the window may be 20 opened, e.g. by a user, so as to be displayed in the GUI, but may also be closed or otherwise not displayed. The image features have one or more characteristics representing one or more hybridization reactions associated with a probe of the probe array.

The GUI of these embodiments also has a second openable window including 25 data features, each relating to one or more quantifications of one or more hybridization reactions associated with a probe of the probe array. This second window may be, for example, a scatter plot of hybridization intensities of probes to two or more labeled samples. The GUI further includes a third openable window including descriptive features such as rows of a spreadsheet. Each row may include 30 descriptive elements associated with a probe. In some implementations, when a user selects a feature from any of the two or more windows, a corresponding feature in at

least one other of the two or more windows is highlighted. For example, a user may select an image feature in the first window (e.g., a spot representing a probe of a spotted array), thereby causing a spot in the scatter plot and a row in the spreadsheet to be highlighted. The spot in the scatter plot and the spreadsheet row provide 5 information about the probe corresponding to the image feature selected by the user in the first window.

The probes may be those of a spotted probe array such as may be generated, for example, by an Affymetrix® 417™ or 427™ Arrayer. As another non-limiting example, the probes may be those synthesized on a synthesized array such as an 10 Affymetrix® GeneChip® array.

With respect to the first window, the graphically represented probes have one or more characteristics indicative of the efficiency or intensity of hybridization associated with the corresponding probe. For example, the intensity or another visual characteristic of the image features graphically representing probes may be varied to 15 indicate the efficiency or intensity of hybridization. With respect to the example of the second window constituting a scatter plot, the plot may show along one axis the intensity of emissions from a first label such as a dye that fluoresces in response a first excitation source. The scatter plot may show along another axis the intensity of emissions from a second dye that fluoresces in response the same or another 20 excitation source. The scatter plot need not be limited to two dimensions, as when, for example, a third dye is associated with probe-target pairs hybridized on the probe array. Any form of labeling may be used, and many types of graphs may be employed that provide, for example, visual comparisons between two or more sets of hybridization data.

25 A third of the two or more windows may include a table, spreadsheet, or other textual or graphical representation of information related to probes in the probe array. In some implementations, for example, a third window may include a spreadsheet having rows (or, in other aspects, columns, or combinations thereof) containing any of a variety of data. For example, the data may relate to the experiment that produced 30 the hybridization intensities represented by a pseudo-image in the first window, e.g., the type of dye or dyes used in the experiment. The data may also include links to

sources, such as on the Internet or another database source, containing information about the probes and/or the targets that hybridized with the probes. As yet another non-limiting example, the data may include statistical information about the absolute or relative intensities of the probes. As a further non-limiting example, the data may 5 include notes, labels, or other information provided by the user.

In some implementations, two or more of the windows are simultaneously displayed to the user on a display device. The user may select a graphical element of one of the simultaneously displayed windows and a corresponding graphical element on another of the two or more windows is highlighted. The highlighting may be done 10 in accordance with any of a variety of known techniques, such as by changing the font and/or color of foreground or background, or by providing special effects such as blinking.

A fourth window may also be opened in some implementations. This fourth window may, like the first window, include image features having one or more 15 characteristics representing one or more hybridization reactions associated with a probe of the probe array. For example, the image features of the first window may have characteristics (such as color or gray-scale intensity) representing the degree, efficiency, or intensity of hybridization of a first sample labeled with a first fluorescent dye to the probes of a spotted array. The image features of the second 20 window may have characteristics representing the degree, efficiency, or intensity of hybridization of a second sample labeled with a second fluorescent dye to the probes of the same spotted array. As another example, the image features of the first window may represent the degree, efficiency, or intensity of hybridization of a first sample labeled with a first fluorescent dye to the probes of a first synthesized array, 25 and the image features of the second window may represent the degree, efficiency, or intensity of hybridization of a second sample labeled with a the same or another fluorescent dye to the probes of a second synthesized array having probes essentially the same as the probes of the first synthesized array.

The characteristics of the image features of the first and/or fourth window may 30 include a chromatic value representing degree, efficiency, or intensity of hybridization. For example, the chromatic value may be a hue (color), brightness,

lightness, or saturation value. The characteristic may also, or in addition, be an intensity value. The intensity value may be, for example, a gray-scale value.

The second openable window may, in some embodiments, include a histogram wherein the plurality of data features comprises bars, each representing a

- 5 quantification of a number of probes having in common a range of degree, efficiency, or intensity of hybridization with one or more targets. The second openable window may also be any other kind of representation of statistical information about absolute or relative hybridization of probes such as may be conveyed, for example, by a scatter plot (as noted), a bar graph, or a line graph.

- 10 With respect to the third openable window, the descriptive features may, as one example, constitute rows of a spreadsheet. Each row may include one or more descriptive elements associated with a probe. Non-limiting examples of descriptive elements include any one or combination of two or more of the following: absolute image intensity value, relative image intensity value, user-supplied data related to the probe, biological information related to the probe; probe identifier, probe x-coordinate identifier, probe y-coordinate identifier, probe-related data, probe data links, pin identifier, and/or well plate identifier. The probe data links may include links to remotely or locally stored user-supplied data related to the probe, and/or links to remotely or locally stored biological information related to the probe. The probe-
15 related data may include chromosome location of a gene or EST represented by the probe, band location on the chromosome, and/or SNP or other marker identifying the location on the chromosome.

- 20 In accordance with other embodiments, a user interface is described that includes any combination of two or more of the following windows: a first window having a plurality of image features, each having one or more characteristics representing one or more hybridization reactions associated with a probe of a probe array; a second window having a plurality of data features, each relating to one or more quantifications of one or more hybridization reactions associated with a probe of the probe array; and a third window having a plurality of descriptive features, each
25 including one or more descriptive elements associated with a probe of the probe array.
30 In these embodiments, when a user selects a feature from any of the two or more

windows, a corresponding feature in at least one other of the two or more windows is highlighted.

In accordance with yet other embodiments, a computer program product is described. This product includes an image processor that processes image data based 5 on scanning a probe array, and a GUI manager constructed and arranged to provide two or more windows. The windows may be any combination of the following: (i) a first window having a plurality of image features based on the processed image data, each having one or more characteristics representing one or more hybridization reactions associated with a probe of the probe array, (ii) a second window having a 10 plurality of data features, each relating to one or more quantifications of one or more hybridization reactions associated with a probe of the probe array, and/or (iii) a third window having a plurality of descriptive features, each including one or more descriptive elements associated with a probe of the probe array. When a user selects a 15 feature from any of the two or more windows, the GUI manager may, in some implementations, cause a corresponding feature in at least one other of the two or more windows to be highlighted.

Also described is a computer program product having a GUI manager that provides two or more windows. These windows may be any combination of (i) a first window having a plurality of image features, each having one or more characteristics 20 representing one or more hybridization reactions associated with a probe of the probe array, (ii) a second window having a plurality of data features, each relating to one or more quantifications of one or more hybridization reactions associated with a probe of the probe array, and (iii) a third window having a plurality of descriptive features, each including one or more descriptive elements associated with a probe of the probe 25 array.

In accordance with yet other embodiments, a method is described that includes providing image data based on scanning a probe array and providing, in a graphical user interface, two or more windows. These windows are selected from the group consisting of (i) a first window having a plurality of image features based on 30 the image data, each having one or more characteristics representing one or more hybridization reactions associated with a probe of a probe array, (ii) a second window

having a plurality of data features, each relating to one or more quantifications of one or more hybridization reactions associated with a probe of the probe array, and (iii) a third window having a plurality of descriptive features, each including one or more descriptive elements associated with a probe of the probe array.

- 5 Also included in the following description is a scanning system that includes a scanner that scans a probe array to generate image data, an image processor that processes the image data, and a GUI manager that provides two or more windows. These windows may be any combination of the following: (i) a first window having a plurality of image features based on the processed image data, each having one or
10 more characteristics representing one or more hybridization reactions associated with a probe of the probe array, (ii) a second window having a plurality of data features, each relating to one or more quantifications of one or more hybridization reactions associated with a probe of the probe array, and (iii) a third window having a plurality of descriptive features, each including one or more descriptive elements associated
15 with a probe of the probe array.

Yet another described embodiment is a scanning system. This system includes a scanner that scans a probe array to generate image data, a computer, and a computer program product. When executed on the computer, the computer program product performs a method comprising the steps of processing the image data and providing,
20 in a graphical user interface, two or more windows. These windows may be any combination of the following: (i) a first window having a plurality of image features based on the processed image data, each having one or more characteristics representing one or more hybridization reactions associated with a probe of a probe array, (ii) a second window having a plurality of data features, each relating to one or
25 more quantifications of one or more hybridization reactions associated with a probe of the probe array, and (iii) a third window having a plurality of descriptive features, each including one or more descriptive elements associated with a probe of the probe array.

Generally, one advantage provided by the preceding and other embodiments is that data regarding probe-target hybridization, and the probes associated with the
30 hybridization reactions, may be simultaneously displayed to a user in a variety of forms. These forms may include, for example, two or more of a pseudo-image of

probe-target hybridization (and probes that did not hybridize with targets); a statistical representation of absolute or relative hybridization (such as in a scatter plot); and/or a table of processed, derived, calculated, retrieved, and/or user-supplied information related to the probes. By selecting a feature corresponding to a probe or probes in one 5 of these windows, other information related to the same probe or probes may be highlighted in the same or other window or windows for the benefit of the user.

According to yet another embodiment, a computer system for providing a user interface with a scanner for scanning a probe array to generate image data includes two or more window means. These window means may include a first window means 10 for providing image feature means having one or more characteristics representing one or more hybridization reactions associated with probe means of a probe array; and a second window means for providing a data feature means related to one or more quantification means of said one or more hybridization reactions associated with probe means of the probe array. These window means may also include a third 15 window means for providing descriptive feature means including one or more descriptive elements associated with probe means of the probe array.

According to yet another embodiment, a computer system for providing a user interface with a scanner for scanning a probe array is programmed to display image features having one or more characteristics representing one or more hybridization 20 reactions associated with a probe of the probe array, data features related to one or more quantifications of one or more hybridization reactions associated with a probe of the probe array, and descriptive features including one or more descriptive elements associated with a probe of the probe array.

According to yet another embodiment, a computer program product includes a 25 GUI manager. The GUI manager is constructed and arranged to provide display regions for displaying image features representing hybridization associated with a probe of a probe array, data features related to quantifying the hybridization associated with a probe of the probe array, and descriptive features associated with a probe of the probe array.

30 According to yet another embodiment, a computer program includes a GUI manager for providing window means for displaying image feature means

representing hybridization means associated with a probe means of a probe array, for displaying data feature means related to quantifying hybridization means associated with probe means of the probe array, and for displaying descriptive feature means associated with probe means of the probe array.

5 The above embodiments, implementations, and aspects are not necessarily inclusive or exclusive of each other and may be combined in any manner that is non-conflicting and otherwise possible, whether they be presented in association with a same, or a different, aspect of the invention. The description of one embodiment, implementation, or aspect is not intended to be limiting with respect to other
10 embodiments or implementations. Also, any one or more function, step, operation, or technique described elsewhere in this specification may, in alternative embodiments or implementations, be combined with any one or more function, step, operation, or technique described in the summary. Thus, the above embodiments, implementations, and aspects are illustrative rather than limiting.

15

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a simplified schematic diagram of one embodiment of networked systems for generating, sharing, and processing probe array data among computers on a network, including an arrayer system for generating spotted probe arrays and
20 scanner systems for scanning spotted and synthesized probe arrays.

Figure 2 is a functional block diagram of one embodiment of a user computer of the networked computers of Figure 1 suitable for controlling the arrayer of Figure 1 to produce spotted arrays.

Figure 3A is a graphical representation of data records in one embodiment of a
25 data file suitable for storing data regarding spotted arrays produced in cooperation with the user computer of Figure 2 and the arrayer of Figure 1.

Figure 3B is a graphical representation of a microscope slide including illustrative embodiments of spotted arrays produced in cooperation with the user computer of Figure 2 and the arrayer of Figure 1.

30 Figure 4 is a simplified graphical representation of selected components of one embodiment of a scanner of Figure 1 suitable for scanning arrays.

Figure 5A is a perspective view of a simplified exemplary configuration of a scanning arm portion of the scanner of Figure 4.

Figure 5B is a top planar view of the scanning arm of Figure 5A as it scans biological features on one embodiment of a spotted array being moved by a
5 translation stage under the arm's arcuate path.

Figure 6A is a graphical representation of one embodiment of a probe feature showing bi-directional scanning lines such as may be implemented using the scanning arm of Figures 5A and 5B.

Figure 6B is an illustrative plot of pixel clock pulses aligned with the scanned
10 probe feature of Figure 6A to show illustrative radial position sampling points.

Figure 6C is an illustrative plot of sampled analog emission voltages aligned with the pixel clock pulses of Figure 6B.

Figure 7 is a functional block diagram of one embodiment of a scanner system of Figure 1.

15 Figure 8 is functional block diagram of one embodiment of a scanner control and analysis application (i.e., computer program product).

Figure 9 is an illustrative implementation of a graphical user interface employed in cooperation with the application of Figure 8.

The described features will be more clearly appreciated from the following
20 detailed description when taken in conjunction with the accompanying drawings. In the drawings, like reference numerals indicate like structures or method steps and the leftmost digit of a reference numeral indicates the number of the figure in which the referenced element first. In functional block diagrams, rectangles generally indicate functional elements, parallelograms generally indicate data, and rectangles with a pair
25 of double borders generally indicate predefined functional elements. In method flow charts, rectangles generally indicate method steps and diamond shapes generally indicate decision elements. All of these conventions, however, are intended to be typical or illustrative, rather than limiting.

DETAILED DESCRIPTION

Systems, methods, and software products to display data from experiments with synthesized and/or spotted arrays are described herein with respect to illustrative, non-limiting, implementations. Various other alternatives, modifications and equivalents are possible. For example, while certain systems, methods, and computer software products are described using exemplary embodiments with reference to spotted arrays analyzed and displayed using Affymetrix® scanners and/or Affymetrix software, the systems, methods, and products of the present invention are not so limited. For example, they generally may be applied with respect to many other probe arrays, including many types of parallel biological assays.

Probe Arrays

For example, certain systems, methods, and computer software products are described herein using exemplary implementations for acquiring, analyzing, and/or displaying data from arrays of biological materials produced by the Affymetrix® 15 417™ or 427™ Arrayers available from Affymetrix, Inc. Other illustrative implementations may be referred to in relation to data from experiments with Affymetrix® GeneChip® arrays. However, these systems, methods, and products may be applied with respect to many other types of probe arrays and, more generally, with respect to numerous parallel biological assays produced in accordance with other 20 conventional technologies and/or produced in accordance with techniques that may be developed in the future. For example, aspects of the systems, methods, and products described herein may, in some implementations, be applied to parallel assays of nucleic acids, PCR products generated from cDNA clones, proteins, antibodies, or many other biological materials. These materials may be disposed on slides (as 25 typically used for spotted arrays), on substrates employed for GeneChip® arrays, or on beads, optical fibers, or other substrates, supports, or media (all or any of which may hereafter generally and collectively be referred to as "substrates"). Some implementations of synthesized arrays, their preparation, substrates, and the like are described in U.S. Patents Nos. 5,744,305 and 5,445,934, which are hereby incorporated herein by reference in their entireties for all purposes. Moreover, with 30 respect to some implementations in which the context so indicates or allows, the

probes need not be immobilized in or on a substrate, and, if immobilized, need not be disposed in regular patterns or arrays. For convenience, the term "probe array" will generally be used broadly hereafter to refer to all of these types of arrays and parallel biological assays.

5 For convenience, an array made by depositing or positioning pre-synthesized or pre-selected probes on a substrate, or by depositing/positioning techniques that may be developed in the future, is hereafter referred to as a "spotted array." Typically, but not necessarily, spotted arrays are commercially fabricated on microscope slides. These arrays often consist of liquid spots containing biological material of potentially
10 varying compositions and concentrations. For instance, a spot in the array may include a few strands of short polymers, such as oligonucleotides in a water solution, or it may include a high concentration of long strands of polymers, such as complex proteins. The Affymetrix® 417™ and 427™ Arrayers, noted above, are devices that deposit densely packed arrays of biological material on a microscope slide in
15 accordance with these techniques. Aspects of these, and other, spot arrayers are described in U.S. Patents Nos. 6,121,048, 6,040,193 and 6,136,269, in PCT Applications Nos. PCT/US99/00730 (International Publication Number WO99/36760) and PCT/US 01/04285, in U.S. Patent Applications Serial Nos. 09/122,216, 09/501,099, and 09/862,177, and in U.S. Provisional Patent Application
20 Serial No. 60/288,403, all of which are hereby incorporated by reference in their entireties for all purposes. Other techniques for depositing or positioning biological probes on a substrate, *i.e.*, creating spotted arrays, also exist. For example, U.S. Patent No. 6,040,193 to Winkler, et al. is directed to processes for dispensing drops of biological material. The '193 patent, and U.S. Patent No. 5,885,837 to Winkler, also
25 describe separating reactive regions of a substrate from each other by inert regions and spotting on the reactive regions. The '193 and '837 patents are hereby incorporated by reference in their entireties. Other techniques for producing spotted arrays are based on ejecting jets of biological material. Some implementations of the jetting technique use devices such as syringes or piezo electric pumps to propel the biological
30 material.

Spotted arrays typically are used in conjunction with tagged biological samples such as cells, proteins, genes or EST's, other DNA sequences, or other biological elements. These samples, referred to herein as "targets," typically are processed so that they are spatially associated with certain probes in the probe array.

- 5 In one non-limiting implementation, for example, one or more chemically tagged biological samples, i.e., the targets, are distributed over the probe array. Some targets hybridize with at least partially complementary probes and remain at the probe locations, while non-hybridized targets are washed away. These hybridized targets, with their "tags" or "labels," are thus spatially associated with the targets' complementary probes. The associated probe and target may sometimes be referred to as a "probe-target pair." Detection of these pairs can serve a variety of purposes, such as to determine whether a target nucleic acid has a nucleotide sequence identical to or different from a specific reference sequence. See, for example, U.S. Patent No. 5,837,832 to Chee, et al. Other uses include gene expression monitoring and
- 10 evaluation (see, e.g., U.S. Patent No. 5,800,992 to Fodor, et al.; U.S. Patent No. 6,040,138 to Lockhart, et al.; and International App. No. PCT/US98/15151, published as WO99/05323, to Balaban, et al.), genotyping (U.S. Patent No. 5,856,092 to Dale, et al.), or other detection of nucleic acids. The '832, '992, '138, and '092 patents, and publication WO99/05323, are incorporated by reference herein in their entirety for all
- 15 purposes.
- 20

To ensure proper interpretation of the term "probe" as used herein, it is noted that contradictory conventions exist in the relevant literature. The word "probe" is used in some contexts in the literature to refer not to the biological material that is deposited on a substrate, as described above, but to what has been referred to herein as the "target." To avoid confusion, the term "probe" is used herein to refer to compounds such as those deposited on a substrate to create spotted arrays, or oligonucleotides on synthesized arrays, as non-limiting examples.

Probe Array Experiment Systems

Figure 1 is a simplified schematic diagram of illustrative systems for generating, sharing, and processing data derived from experiments using probe arrays (*i.e.*, spotted arrays and/or synthesized arrays). More particularly, an illustrative

arrayer system 148 and illustrative scanner systems 150A and 150B (collectively, scanner systems 150) are shown. Arrayer system 148 includes arrayer 120 that may be any type of arrayer for depositing probes to create spotted arrays such as, for example, the Affymetrix 417™ or 427™ Arrayers noted above. Further details of 5 illustrative arrayers are provided in U.S. Patent Application Serial No. 09/682,076, hereby incorporated by reference in its entirety for all purposes. In the presently illustrated example, data may be communicated among user computer 100A of system 148, user computers 100B and 100C of systems 150, and Laboratory Information Management (LIMS) server 120 over network 125. LIMS server 120 and associated 10 software generally provides data capturing, tracking, and analysis functions from a centralized infrastructure. Aspects of a LIMS are described in U.S. Provisional Patent Application Nos. 60/220,587 and 60/273,231, both of which are hereby incorporated by reference herein for all purposes. LIMS server 120 and network 125 are optional, and the systems in other implementations may include a scanner for spotted arrays 15 and not synthesized arrays, or vice versa. Also, rather than employing separate user computers 100A and 100B to operate and process data from an arrayer and scanner, respectively, as in the illustrated implementation, a single computer may be used for all of these purposes in other implementations. More generally, a large variety of computer and/or network architectures and designs may be employed, and it will be 20 understood by those of ordinary skill in the relevant art that many components of typical computer network systems are not shown in Figure 1 for sake of clarity.

User Computer 100A

As shown in Figure 1 and noted above, arrayer 120 operates in the illustrated implementation under computer control, e.g., under the control of user computer 25 100A. Although computer 100A is shown in Figure 1 for clarity as being directly coupled to arrayer 120, it may alternatively be coupled to arrayer 120 over a local-area, wide-area, or other network, including an intranet and/or the Internet.

Figure 2 is a functional block diagram showing an illustrative implementation of computer 100A. Computer 100A may be a personal computer, a workstation, a 30 server, or any other type of computing platform now available or that may be developed in the future. Typically, computer 100A includes known components such

as processor (e.g., CPU) 205, operating system 210, system memory 220, memory storage devices 225, graphical user interface (GUI) controller 215, and input-output controllers 230, all of which typically communicate in accordance with known techniques such as via system bus 204. It will be understood by those skilled in the relevant art that there are many possible configurations of the components of computer 100A and that some components that may typically be included in computer 100A are not shown, such as cache memory, a data backup unit, and many other devices.

Input-output controllers 230 could include any of a variety of known devices for accepting and processing information from a user, whether a human or a machine, whether local or remote. Such devices include, for example, modem cards, network interface cards, sound cards, or other types of controllers for any of a variety of known input devices. Output controllers of input-output controllers 230 could include controllers for any of a variety of known display devices for presenting information to a user, whether a human or a machine, whether local or remote. If one of these display devices provides visual information, this information typically may be logically and/or physically organized as an array of picture elements, sometimes referred to as pixels. GUI controller 215 may comprise any of a variety of known or future software programs for providing graphical input and output interfaces between computer 100A and a user 201 (*e.g.*, an experimenter wishing to use arrayer 120 to generate spotted arrays), and for processing inputs from user 201 (hereafter sometimes referred to as user inputs or user selections).

Arrayer Manager Application 290

Arrayer manager application 290 of the illustrated implementation is a software application that controls functions of arrayer 120 and processes data supplied by user 201. As more particularly described with respect to certain implementations in U.S. Provisional Patent Application Serial No. 60/288,403, incorporated by reference above, application 290, when executed in coordination with processor 205, operating system 210, and/or GUI controller 215, performs user interface functions, data processing operations, and data transfer and storage operations. For example, with respect to user interface functions, user 201 may employ one or more of GUI's

282 to specify and describe particular clones and their location in particular wells of particular well plates. Using another of GUI's 282, user 201 may specify how spots of the clones are to be arranged in arrays on one or more slides, as described in greater detail below with respect to fields 304 and 306 of array content file 292 shown in
5 Figure 3A. Yet another of GUI's 282 may be used to operate arrayer 120, e.g., to initiate the spotting of a number of slides without further user participation.

As will be evident to those skilled in the relevant art, application 290 may be loaded into system memory 220 and/or memory storage device 225 through an input device of devices 280. Alternatively, application 290 may be implemented as
10 executable instructions stored in firmware. Executable code corresponding to application 290 is referred to as arrayer manager application executable 290' and is shown for convenience with respect to the illustrated implementation as stored in system memory 220. However, instructions and data including executable instructions of application 290, and data used or generated by it, may be located in or
15 shifted among other memory devices, local or remote, as convenient for data storage, data retrieval, and/or execution.

Figure 3A is a graphical representation of illustrative data records in one implementation of a data file generated by arrayer manager application executable 290'. The data file in this illustration, referred to as array content file 292, consists of
20 records 301, each one of which (i.e., records 301A through 301N for any number of N records) corresponds to one of N spots, i.e., probes that have been deposited, or are planned to be deposited, on spotted arrays 121. For example, with reference to the graphical representation of spotted arrays 121 shown in Figure 3B, two arrays 121A and 121B (collectively, arrays 121) have been printed on microscope slide substrate
25 333 by arrayer 120. Array 121A includes probe 370A. It is assumed for purposes of illustration that data relating to probe 370A is stored by executable 290' in probe record 301A. In this example, each of the records in file 292 includes the following illustrative fields: probe identifier(s) 302, probe x-coordinate identifier(s) 304, probe y-coordinate identifier(s) 306, probe data 308, probe data links 310, pin identifier 312,
30 well plate identifier 316, and user-supplied data 320.

The field in record 301A labeled probe identifier(s) 302A thus, in this example, includes certain information related to the identification of probe 370A. For instance, field 302A may include a name for cDNA deposited by a pin of arrayer 120 in array 121A to produce probe 370A. In various implementations, field 302A may

5 also, or in addition, include a nucleotide identifier and/or a gene symbol that identifies probe 370A. Also, field 302A may include a build or release number of a database so that the data source used to develop the probe can be identified. As yet another example of information that may be included in field 302A, a probe may be identified as either an original or as a replicate. For instance, for quality control or other

10 reasons, probe 370B of array 121A may be the same probe as probe 370A, or a number of such replicate probes may be deposited. The designation of original or replicate number assists in comparing results from probes that are based on the same sample. As one of ordinary skill in the relevant art will readily appreciate, all or some of this identifying data may be stored as a single value in field 302A (such as,

15 for example, concatenating name, nucleotide identifier, etc.), in separate fields (e.g., 302A', 302A", etc., not shown), in linked fields, and so on as may be convenient for data storage and/or processing. The other fields described below similarly are only representative of many possible storage and data retrieval architectures.

Field 308A, labeled probe data in this example, may include probe-related data

20 such as the chromosome location of the gene or EST represented by the probe, the band location on the chromosome, a SNP or other type of marker that can identify the location on the chromosome, and so on. Field 310A, labeled probe data links in this example, similarly may include an accession number from GenBank, a UniGene cluster number, and/or another identifier that facilitates access to data related to probe

25 370A that is stored in a database. This database may, but need not, be external to computer 100A and accessed via network 125 and/or the Internet or other network. Systems for providing access to such information are described, for example, in U.S. Provisional Patent Application, Serial No. 60/288,429, hereby incorporated herein by reference in its entirety. Field 312A of this example identifies the pin on the print

30 head(s) that is used to deposit probe 370A onto the slide. This information may be useful in comparing probes deposited with the same pin to determine, for example, if

the pin is defective. Fields 314A and 316A contain information that respectively identifies the well plate and particular well from which biological fluid was taken to create probe 370A. Field 320A may contain a variety of data supplied by user 201 such as the user's name, the data of the experiment, and so on. It will be understood 5 that there are many other types of data relating to probe 370A that may be stored, and that numerous alternative arrangements may be implemented for storing them.

Fields 304A and 306A are used to identify the location of probe 370A on the slide in x and y coordinates, respectively. It will be understood that other coordinate systems (e.g., radial system) could be used, and that the definition of the orientation 10 and zero points of the coordinate references of the present example are illustrative only. In one implementation of the present example, field 304A could include primary and secondary row coordinates, and field 306A could include primary and secondary column coordinates, that identify the position of probe 370A. For instance, arrays 121A and 121B could be viewed as arranged in a single primary column 15 (disposed horizontally in Figure 3B) in which array 121A occupies the first primary row and array 121B occupies the second primary row. Such an implementation may be said to involve relative, rather than absolute, locations because locations of probes are specified in relation to each other rather than in relation to a reference point on the substrate. It may be advantageous in some implementations to specify absolute, rather 20 than relative, locations. In one such implementation, orthogonal x and y axes could be defined in relation to the sides of the microscope slide, such as x axis 392 and y axis 394 of the illustrated example, with the 0,0 reference coordinates defined with reference to a particular point on the slide. For instance, some slides are manufactured with a frosted area, such as area 380 of this example, so that a user may 25 more easily label or write on the slide, or for other reasons. A particular point at a corner of the frosted area could readily be defined as the reference coordinate, or any of various other methods could be used to specify a reference coordinate on, or spatially related to, a point on the substrate.

Scanner 160A: Optics and Detectors

30 Any of a variety of conventional techniques, or ones to be developed in the future, may be used to generate probe-target pairs in probe arrays that may be detected

using a scanner. As one illustrative example that will be familiar to those of ordinary skill in the relevant art, conventional fluidics stations, hybridization chambers, and/or various manual techniques (as, for example, generally and collectively represented by hybridization process 122 in Figure 1) may be used to apply one or more labeled targets to spotted arrays on microscope slides. In a particular implementation, for instance, sample of a first target may be labeled with a first dye (an example of what may more generally be referred to hereafter as an "emission label") that fluoresces at a particular characteristic frequency, or narrow band of frequencies, in response to an excitation source of a particular frequency. A second target may be labeled with a second dye that fluoresces at a different characteristic frequency. The excitation source for the second dye may, but need not, have a different excitation frequency than the source that excites the first dye, e.g., the excitation sources could be the same, or different, lasers. The target samples may be mixed and applied to the probes of spotted arrays on microscope slides, and conditions may be created conducive to hybridization reactions, all in accordance with known techniques. In accordance with other techniques, such as typically are applied with respect to Affymetrix® GeneChip® synthesized arrays, samples of one labeled target are applied to one array and samples of a second labeled target are applied to a second array having the same probes as the first array. Hybridization techniques are applied to both arrays. For example, synthesized arrays 134 of Figure 1 may be illustratively assumed to be two GeneChip® synthesized arrays that have been subject to hybridization processes with respect to two different target samples, each labeled with different fluorescent dyes. See, e.g., U.S. Patent No. 6,114,122, which is hereby incorporated by reference herein in its entirety.

Many scanner designs may be used to provide excitation signals to excite labels on targets or probes, and to detect the emission signals from the excited labels. In references herein to illustrative implementations, the term "excitation beam" may be used to refer to light beams generated by lasers to provide the excitation signal. However, excitation sources other than lasers may be used in alternative implementations. Thus, the term "excitation beam" is used broadly herein. The term "emission beam" also is used broadly herein. As noted, a variety of conventional

scanners detect fluorescent or other emissions from labeled target molecules or other material associated with biological probes. Other conventional scanners detect transmitted, reflected, refracted, or scattered radiation from such targets. These processes are sometimes generally and collectively referred to hereafter for convenience simply as involving the detection of "emission beams." The signals detected from the emission beams are generally referred to hereafter as "emission signals" or "emissions," and these terms are intended to have a broad meaning commensurate with that intended herein for the term "emission beams."

Various detection schemes are employed depending on the type of emissions and other factors. A typical scheme employs optical and other elements to provide an excitation beam, such as from a laser, and to selectively collect the emission beams. Also generally included are various light-detector systems employing photodiodes, charge-coupled devices, photomultiplier tubes, or similar devices to register the collected emission beams. For example, a scanning system for use with a fluorescently labeled target is described in U.S. Pat. No. 5,143,854, hereby incorporated by reference in its entirety for all purposes. Other scanners or scanning systems are described in U.S. Patent Nos. 5,578,832, 5,631,734, 5,834,758, 5,936,324, 5,981,956, 6,025,601, 6,141,096, 6,185,030, 6,201,639, 6,218,803, and 6,252,236; in PCT Application PCT/US99/06097 (published as WO99/47964); in U.S. Patent Application, Serial No. 09/681,819; and in U.S. Provisional Patent Application Serial No. 60/286,578, each of which also is hereby incorporated herein by reference in its entirety for all purposes.

Figure 4 is a simplified graphical representation of selected components of an illustrative type of scanner 160A suitable for scanning hybridized spotted arrays 132A and 132B disposed on slide 333 (i.e., in this example, spotted arrays 121A and 121B, respectively, after hybridization process 122). These illustrative components, which will be understood to be non-limiting and not exhaustive, are referred to collectively for convenience as scanner optics and detectors 400. Scanner optics and detectors 400 include excitation sources 420A and 420B (collectively referred to as excitation sources 420). Any number of one or more excitation sources 420 may be used in alternative embodiments. In the present example, sources 420 are lasers; in

particular, source 420A is a diode laser producing red laser light having a wavelength of 635 nanometers and, source 420B is a doubled YAG laser producing green laser light having a wavelength of 532 nanometers. Further references herein to sources 420 generally will assume for illustrative purposes that they are lasers, but, as noted, 5 other types of sources, e.g., x-ray sources, may be used in other implementations.

Sources 120A and 120B may alternate in generating their respective excitation beams 435A and 435B between successive scans, groups of successive scans, or between full scans of an array. Alternatively, both of sources 120 may be operational at the same time. For clarity, excitation beams 435A and 435B are shown as distinct 10 from each other in Figure 4. However, in practice, turning mirror 424 and/or other optical elements (not shown) typically are adjusted to provide that these beams follow the same path.

Scanner optics and detectors 400 also includes excitation filters 425A and 425B that optically filter beams from excitation sources 420A and 420B, respectively. 15 The filtered excitation beams from sources 420A and 420B may be combined in accordance with any of a variety of known techniques. For example, one or more mirrors, such as turning mirror 424, may be used to direct filtered beam from source 420A through beam combiner 430. The filtered beam from source 420B is directed at an angle incident upon beam combiner 430 such that the beams combine in 20 accordance with optical properties techniques well known to those of ordinary skill in the relevant art. Most of combined excitation beams 435 are reflected by dichroic mirror 436 and thence directed to periscope mirror 438 of the illustrative example. However, dichroic mirror 436 has characteristics selected so that portions of beams 435A and 435B, referred to respectively as partial excitation beams 437A and 437B 25 and collectively as beams 437, pass through it so that they may be detected by excitation detector 410, thereby producing excitation signal 494.

In the illustrated example, excitation beams 435 are directed via periscope mirror 438 and arm end turning mirror 442 to an objective lens 445. As shown in Figures 5A and 5B, lens 445 in the illustrated implementation is a small, light-weight 30 lens located on the end of an arm that is driven by a galvanometer around an axis perpendicular to the plane represented by galvo rotation 449 shown in Figure 4.

Objective lens 445 thus, in the present example, moves in arcs over hybridized spotted arrays 132 disposed on slide 333. Fluorophores in hybridized probe-target pairs of arrays 132 that have been excited by beams 435 emit emission beams 452 (beam 452A in response to excitation beam 435A, and beam 452B in response to excitation beam 435B) at characteristic wavelengths in accordance with well-known principles. Emission beams 452 in the illustrated example follows the reverse path as described with respect to excitation beams 435 until reaching dichroic mirror 436. In accordance with well-known techniques and principles, the characteristics of mirror 436 are selected so that beams 452 (or portions of them) pass through the mirror rather than being reflected.

In the illustrated implementation, filter wheel 460 is provided to filter out spectral components of emission beams 452 that are outside of the emission band of the fluorophore, thereby providing filtered beams 454. The emission band is determined by the characteristic emission frequencies of those fluorophores that are responsive to the frequencies of excitation beams 435. In accordance with techniques well known to those of ordinary skill in the relevant arts, including that of confocal microscopy, filtered beams 454 may be focused by various optical elements such as lens 465 and also passed through illustrative pinhole 467 or other element to limit the depth of field, and thence impinges upon emission detector 415.

Emission detector 415 may be a silicon detector for providing an electrical signal representative of detected light, or it may be a photodiode, a charge-coupled device, a photomultiplier tube, or any other detection device that is now available or that may be developed in the future for providing a signal indicative of detected light. For convenience of illustration, detector 415 will hereafter be assumed to be a photomultiplier tube (PMT). Detector 415 thus generates emission signal 492 that represents numbers of photons detected from filtered emission beam 454.

Figure 5A is a perspective view of a simplified representation of the scanning arm portion of scanner optics and detectors 400. Arm 500 moves in arcs around axis 510, which is perpendicular to the plane of galvo rotation 449. A position transducer 515 is associated with galvanometer 515 that, in the illustrated implementation, moves arm 500 in bi-directional arcs. Transducer 515, in accordance with any of a variety of

known techniques, provides an electrical signal indicative of the radial position of arm 500. Certain non-limiting implementations of position transducers for galvanometer-driven scanners are described in U.S. Patent No. 6,218,803, which is hereby incorporated by reference in its entirety for all purposes. The signal from transducer 515 is provided in the illustrated implementation to user computer 100B so that clock pulses may be provided for digital sampling of emission signal 492 when arm 500 is in certain positions along its scanning arc.

5 Arm 500 is shown in alternative positions 500' and 500" as it moves back and forth in scanning arcs about axis 510. Excitation beams 435 pass through objective lens 445 on the end of arm 500 and excite fluorophore labels on targets hybridized to certain of probes 370 in arrays 132 disposed on slide 333, as described above. The 10 arcuate path of excitation beams 435 is schematically shown for illustrative purposes as path 550. Emission beams 452 pass up through objective lens 445 as noted above. Slide 333 of this example is disposed on translation stage 542 that is moved in what is 15 referred to herein as the "y" direction 544 so that arcuate path 550 repeatedly crosses the plane of arrays 132.

Figure 5B is a top planar view of arm 500 with objective lens 445 scanning arrays 132 as translation stage 542 is moved under path 550. As shown in Figure 5B, 20 arcuate path 550 of this example is such that arm 500 has a radial displacement of θ in each direction from an axis parallel to direction 544. What is referred to herein as the "x" direction, perpendicular to y-direction 544, is shown in Figure 5B as direction 543. Further details of confocal, galvanometer-driven, arcuate, laser scanning instruments suitable for detecting fluorescent emissions are provided in PCT Application PCT/US99/06097 (published as WO99/47964) and in U.S. Patents Nos. 25 6,185,030 and 6,201,639, all of which have been incorporated by reference above. It will be understood that although a galvanometer-driven, arcuate, scanner is described in this illustrative implementation, many other designs are possible, such as the voice-coil-driven scanner described in U.S. Patent Application, Serial No. 09/383,986, hereby incorporated herein by reference in its entirety for all purposes.

30 Figure 6A is a simplified graphical representation of illustrative probe 370A as it is scanned by scanner 160A. It is assumed for illustrative purposes that probe 370A

has hybridized with a fluorescently labeled target. Although Figure 6A shows probe 370A in idealized form, i.e. a perfect circle, it will be understood that many shapes, including irregular shapes, are possible.

In the manner described above, objective lens 445 scans over probe 370A (and 5 other probes of arrays 132) in bi-directional arcs. An illustrative scan 620 is shown in Figure 6A, which is not necessarily drawn to scale; e.g., the ratio of the radius of the arc of scan 620 to the radius of probe 370A is illustrative only. As also noted, probe 370A moves under objective lens 445 carried by translation stage 542 in y-direction 544. In particular, in the illustrated implementation, arm 500 scans in an arc in one 10 direction, shown as left-to-right scan 620 in Figure 6A. Translation stage 542 is then moved incrementally by a stepping motor (not shown) in y-direction 544 and arm 500 then scans back in the opposite direction, shown as right-to-left arcuate scan 622. Translation stage 542 is again moved in direction 544, and so on in scan-step-scan-step sequences. The distance between scans 620 and 622 thus corresponds to the 15 distance that translation stage 542 is moved in each increment, although it will be understood that the distance shown in Figure 6A is not necessarily to scale and is illustrative only. It will be understood that any other combination of scanning and stepping is possible in alternative implementations, and that scanning and moving of translation stage 542 may occur at the same or at overlapping times in some 20 implementations. Translation stage 542 need not be stepped in some implementations, but may, for example, be moved continuously.

Figure 6B is a plot having a pixel clock axis 630 showing when clock pulses 632 occur. Clock pulses 632 may be generated by a pixel clock of scanner 160A (e.g., complex programmable logic device 830, described below) or, alternatively, they may 25 be generated by software executing in computer 100B (e.g., executable 790', described below). Axis 630 in the illustrated implementation is a spatial axis; that is, each of clock pulses 632 occurs in reference to the radial location of arm 500 during each scan, as described in greater detail below. Thus, with reference to the position of translation stage 542 indicated by scan 620, a clock pulse 632A occurs prior to arm 30 500 passing over probe 370A from the left as shown in Figures 6A and 6B. (For sake of clarity of illustration only, vertical dotted lines are provided between Figures 6A

and 6B, and between Figures 6B and 6C, to illustrate the alignment of these figures.) As another example, clock pulse 632C occurs with respect to scan 620 when arm 500 has just passed over portions of probe 370A indicated by pixel areas 610A and 610B. These areas are referred to as pixel areas because a digital value is assigned to each 5 such area in the illustrated implementation based on the strength of a processed emission signal associated with that area. In accordance with known techniques, clock pulses 632 enable the digital sampling of the processed emission signal.

As noted, clock pulses 632 are spatially rather than temporally determined in the illustrated implementation. Moreover, in some aspects of the illustrated 10 implementation, galvanometer 516 is driven by a control signal provided by user computer 100B such that the velocity of arm 500 in x-direction 444 is constant in time during those times when arm 500 is over probe 370A (and, typically, over other of probes 370 of arrays 132 as they are scanned). That is, dx/dt is a constant (and thus the angular velocity varies) over the probe-scanning portions of each arc and, in 15 particular, it is a constant during the times when clock pulses are generated to enable digital sampling. As is evident, dx/dt must be reduced to zero between each successive scan, but this deceleration and reversal of direction takes place after arm 500 has passed over probe 370A (or, more generally, array 132A or 132B). The design and implementation of a galvanometer control signal to provide constant dx/dt 20 are readily accomplished by those of ordinary skill in the relevant art.

Thus, the approximate sampling rate may readily be calculated based on the desired scanning speed (dx/dt) and desired pixel resolution. To provide an illustrative example, a spot deposited by an Affymetrix® 417™ or 427™ Arrayer typically has a diameter of approximately 150 to 200 microns. Spotted arrays made using these 25 instruments typically may be deposited over a surface having a width of about 22 millimeters on a microscope slide that is 25 millimeters wide. In order to achieve pixel resolution of about 10 microns, a sampling rate of about 160 kHz is sufficient for scanning speeds typical for scanners used with respect to these probe arrays, such as the Affymetrix® 428™ scanner. Other sampling rates, readily determined by those 30 of ordinary skill, may be used in other applications in which, for example, different scanning speeds are used and/or different pixel resolutions are desired. The desired

pixel resolution typically is a function of the size of the probe features, the possibility of variation in detected fluorescence within a probe feature, and other factors.

- Figure 6C shows digital values representative of emission signal 492 as sampled at (and/or collected for an adjoining period before) points on scans 620 and 622 represented by constant radial position lines 625A-K (collectively referred to as radial position lines 625). The voltages sampled during scan 620 are shown as dots, while the voltages sampled during scan 622 are shown as x's. The determination of when to initiate pixel clock signals may be made using position transducer 515, as described in greater detail in U.S. Provisional Patent Application Serial No. 60/286,578, incorporated by reference above. Thus, for example, voltage 650C of Figure 6C is representative of emission signal 492 based on sampling enabled by a pixel clock pulse at point 632C on axis 630 that is triggered when arm 500 is at radial position 625C during scan 620. After translation stage 542 has been incremented, voltage 652C is sampled during scan 622 at the same radial position, shown as radial position 625C".

User Computer 100B

- As shown in Figure 1 and noted above, scanner 160B operates in the illustrated implementation under computer control, e.g., under the control of user computer 100B, as shown in greater detail in Figure 7. Although computer 100B is shown in Figures 1 and 7 for clarity as being directly coupled to scanner 160A, it may alternatively be coupled to scanner 160A over a local-area, wide-area, or other network, including an intranet and/or the Internet. Computer 100B may be a personal computer, a workstation, a server, or any other type of computing platform now available or that may be developed in the future. Typically, computer 100B includes known components such as processor (e.g., CPU) 705, operating system 710, system memory 720, memory storage devices 725, GUI controller 715, and input-output controllers 730, all of which typically communicate in accordance with known techniques such as via system bus 704. It will be understood by those skilled in the relevant art that there are many possible configurations of the components of computer 100B and that some components that may typically be included in computer

100B are not shown, such as cache memory, a data backup unit, and many other devices.

Input-output controllers 730 could include any of a variety of known devices for accepting and processing information from a user, whether a human or a machine, 5 whether local or remote. Such devices include, for example, modem cards, network interface cards, sound cards, or other types of controllers for any of a variety of known input devices. Output controllers of input-output controllers 730 could include controllers for any of a variety of known display devices for presenting information to a user, whether a human or a machine, whether local or remote. If one of these 10 display devices provides visual information, this information typically may be logically and/or physically organized as an array of picture elements, sometimes referred to as pixels. Graphical user interface (GUI) controller 715 may comprise any of a variety of known or future software programs for providing graphical input and output interfaces between computer 100B and a user 701 (e.g., an experimenter 15 wishing to use scanner 160A to acquire and analyze information from spotted arrays), and for processing inputs from user 701 (hereafter sometimes referred to as user inputs or user selections). To avoid confusion, references hereafter to a "GUI" generally are directed to one or more graphical user interfaces displayed on a display device of devices 780 to user 701, such as GUI 782A of Figures 8 and 9, described 20 below. To be distinguished are references to a "GUI controller," such as GUI controller 715, that operates to display the GUI's to user 701 and to process input information provided by user 701 through the GUI's. As is well known in the relevant art, a user may provide input information using a GUI by selecting, pointing, typing, speaking, and/or otherwise operating, or providing information into, one or 25 more input devices of devices 780 in a known manner.

Computer 100B may optionally include process controller 740 that may, for example, be any of a variety of PC-based digital signal processing (DSP) controller boards, such as the M44 DSP Board made by Innovative Integration of Simi Valley, California. More generally, controller 740 may be implemented in software, hardware 30 or firmware, or any combination thereof.

Scanner Control and Analysis Application 790

Scanner control application 790 of the illustrated implementation is a software application that controls functions of scanner 160A. In addition, when executed in coordination with processor 705, operating system 710, GUI controller 715, and/or process controller 740, application 790 performs user interface functions, data and image processing operations, and data transfer and storage operations related to data provided by or to scanner 160A and/or user 701, as described in greater detail below. Affymetrix® Jaguar™ software, available from Affymetrix, Inc., is a commercial product that, in some implementations, includes various aspects of application 790.

- 10 As more particularly shown in Figure 8, scanner control application 790 in the illustrated implementation includes a GUI manager 810 that, in accordance with known techniques, receives and processes user selections of windows for display and user selections of features within one or more of the displayed windows. GUI manager 810 also builds and displays, in accordance with known techniques, the
- 15 windows, features, and selections according to templates and other stored data as well as user data 794, array data 792, image data 798, and image analysis data 799. Also included in application 790 is image processor 820 that receives image data 798 from scanner 160A. In particular, in the illustrative implementation image analyzer 852 of processor 820 receives data 798 and analyzes it to provide image analysis data 799.
- 20 Data 799 is stored by storer 855 in system memory 720 and also provided to GUI manager 810 for inclusion in GUI 782A. Similarly, image data 798 may be provided to GUI manager 810 for inclusion in GUI 782A.

- For convenience of further description, it is illustratively assumed that user 701 indicates that three openable windows are to be displayed, as represented by
- 25 illustrative GUI 782A of Figure 8 and shown in greater detail in Figure 9. It will be understood that GUI 782A of Figure 9 is illustrative only, and that numerous variations, alternative, and/or rearrangements of the information and features described herein with respect to GUI 782A may be provided in other implementations.

- 30 It will be illustratively assumed that user 701 selects three openable windows to be displayed in GUI 782A. This selection may be accomplished in accordance with

a variety of known techniques, such as by selecting the windows from a pull down menu, e.g., from "View" menu 960 of Figure 9. As shown in Figure 9, GUI 782A of this example thus includes first window 905 that includes a plurality of image features, referred to for convenience as spots 951, such as spots 951A-D. Spots 951 of this implementation may be considered to be pseudo-images of probes in one or more spotted arrays. Thus, for example, a visual characteristic of image feature 951A represents a hybridization reaction associated with a probe of a spotted array arranged in the upper left quadrant of first window 905. Spots 951B and 951C are associated with another spotted array, the pseudo-image of which is arranged in the upper right quadrant. Similarly, spot 951D is associated with a third spotted array, the pseudo-image of which is arranged in the lower right quadrant of first window 905. In this example, the visual characteristic may be the gray-scale intensity of spots 951. Many of spots 951 appear of equal intensity in this example, but it will be understood that this is a simplification for convenience of illustration only. In general, the intensity or other visual or other characteristic of spots 951 may vary to represent a degree, efficiency, or intensity of hybridization of a probe-target pair.

It is also illustratively assumed with respect to GUI 782A of Figure 9 that user 701 has selected to display, i.e., open, second openable window 907 that, in this illustrative implementation, is a scatter plot or graph. Window 907 includes a plurality of data features 952, such as represented in this example by dots 952 including dots 952A-D. The placement of each of dots 952 in relation to horizontal axis 956 and vertical axis 957 of the scatter plot indicates, in this example, the intensity of hybridization of a probe in relation to emissions from a first dye attached, for example, to a first target and emissions from a second dye attached to a second target. For instance, the placement of dot 952A in relation to axis 956 indicates the intensity of an emission signal due to the probe associated with dot 952A hybridizing to a first target labeled with the first dye, and the placement of dot 952A in relation to axis 957 indicates the intensity of an emission signal due to the same probe hybridizing to a second target labeled with the second dye. In this implementation, the intensities of the emission signals, and thus the plot of window 907, are provided

in log scale. However, other scales, such as linear scale, may be employed in other implementations.

In the illustrative implementation, second window 907 is displayed by overlaying it on top of first window 905. However, in alternative implementations, 5 the windows may be displayed without overlapping or overlaying, in accordance with known techniques. Also in accordance with known techniques, any of the windows may be resized, moved, or rearranged by user 701.

It is further assumed that user 701 has selected to display third window 906 that, in this implementation, is a spreadsheet. The spreadsheet includes a plurality of 10 descriptive features, i.e., rows in this example. Thus, for instance, row 953A is shown that provides information about a probe in the scanned probe array. The descriptive elements in this row, each arranged in a separate column, include, for example, a “Row” element having a value “1” and a “Col” element having a value “8.”

It is assumed for illustrative purposes that user 701 selects row 953A. GUI 15 manager 810 causes row 953A to be highlighted in accordance with known techniques. GUI manager 810 has populated row 953A (and the other displayed rows of the spreadsheet) with information available to manager 810 from array data 792, user data 794, image data 798 and/or image analysis data 799. For example, in the illustrated example, the values “1” in the “Row” column and “8” in the “Col” column 20 indicate that the probe associated with row 953A is located in the first row and eighth column of the probe array. Other of array data 792, e.g., primary rows and columns as described above, may be provided in alternative examples to indicate which of the arrays shown in window 905 constitute the array in which the probe corresponding to row 953A is located. As additional examples, the value of the descriptive element of 25 row 953A arranged under the column labeled “Cy3 Signal” indicates an intensity of the emission signal from the dye Cy3 detected by scanner 160A by scanning the probe associated with row 953A.

In accordance with some implementations of the present invention, GUI manager 810 automatically highlights the features of window 905 and window 907 30 corresponding to the user-selected and highlighted feature of window 906. Thus, as shown in GUI 782A of Figure 9, GUI manager 810 causes spot 951A of window 905

to be highlighted (i.e., in this example a white circle highlights the spot's boundaries) and causes dot 952A of window 907 to be highlighted (i.e., a circle is drawn around it in this example). In addition, in this implementation textual element 955 is provided at the bottom of window 907 that shows intensity information related to the
5 highlighted dot 952A. The preceding illustrative description could also have assumed that user 701 selected spot 951A, thus causing GUI manager 810 to highlight row 953A and dot 952A, or that user 701 selected dot 952A, causing GUI manager 810 to highlight row 953A and spot 951A. In any of these cases, dot 952A, textual element 955, spot 951A, and row 953A all provide user 701 with easily accessible and
10 correlated information regarding a common probe. Advantageously, this information may be displayed to user 701 in simultaneously displayed windows on GUI 782A. In other examples, user 701 may have selected any two of the three illustrative windows described above.

Additional embodiments are described in the copending PCT Application
15 PCT/US01/ ____ entitled "System Method and Software Product for Controlling Biological Microarray Scanner" filed on 22 August 2001, which is incorporated by reference as if fully provided herein.

Having described various embodiments and implementations of the present invention, it should be apparent to those skilled in the relevant art that the foregoing is
20 illustrative only and not limiting, having been presented by way of example only. Many other schemes for distributing functions among the various functional elements of the illustrated embodiment are possible in accordance with the present invention. The functions of any element may be carried out in various ways in alternative embodiments. Also, the functions of several elements may, in alternative
25 embodiments, be carried out by fewer, or a single, element.

For example, arrayer manager application 290 is described as executing on computer 100A that controls arrayer 120, and scanner control application 390 is described as executing on computer 100B that control scanner 160A. However, aspects of the invention need not be divided into these distinct functional elements.
30 Rather, for example, applications 290 and 390 could be executed on a same computer that may, for example, control both arrayer 120 and scanner 160A. Moreover,

applications 290 and 390 may be part of a same computer program product irrespective of whether they are executed on a same, or different, computers.

In addition, it will be understood by those skilled in the relevant art that control and data flows between and among functional elements of the invention and 5 various data structures may vary in many ways from the control and data flows described above. More particularly, intermediary functional elements (not shown) may direct control or data flows, and the functions of various elements may be combined, divided, or otherwise rearranged to allow parallel processing or for other reasons. Also, intermediate data structures or files may be used, various described 10 data structures or files may be combined, the sequencing of functions or portions of functions generally may be altered, and so on. Numerous other embodiments, and modifications thereof, are contemplated as falling within the scope of the present invention as defined by appended claims and equivalents thereto.

15 Copyright Statement

A portion of the disclosure of this patent document contains material that is subject to copyright protection. The copyright owner has no objection to the facsimile reproduction by anyone of the patent document or the patent disclosure as it appears in any Patent Office patent file or records, but otherwise reserves all copyright rights 20 whatsoever.

What is claimed is:

CLAIMS

1. A user interface, comprising:
 - a first openable window having a plurality of first image features, each having one or more characteristics representing one or more hybridization reactions
 - 5 associated with a probe of a probe array;
 - a second openable window having a plurality of data features, each relating to one or more quantifications of one or more hybridization reactions associated with a probe of the probe array; and
 - a third openable window having a plurality of descriptive features, each 10 including one or more descriptive elements associated with a probe of the probe array.
2. The user interface of claim 1, wherein the probe array comprises a spotted array.
- 15 3. The user interface of claim 1, wherein the probe array comprises a synthesized array.
4. The user interface of claim 1, wherein the first, second, and third openable windows are all open in the interface at a same time.
- 20 5. The user interface of claim 1, further comprising:
 - a fourth openable window having a plurality of second image features, each having one or more characteristics representing one or more hybridization reactions associated with a probe of the probe array.
- 25 6. The user interface of claim 5, wherein the first image features are generated based on emissions of a first wavelength and the second image features are generated based on emissions of a second wavelength different from the first wavelength.

7. The user interface of claim 1, wherein the one or more characteristics of the plurality of first image features include a chromatic value representing degree, efficiency, or intensity of hybridization.

5 8. The user interface of claim 7, wherein the chromatic value is a hue, brightness, lightness, or saturation value.

9. The user interface of claim 1, wherein the one or more characteristics of the plurality of first image features include an intensity value representing degree, 10 efficiency, or intensity of hybridization.

10. The user interface of claim 9, wherein the intensity value includes a gray-scale value.

15 11. The user interface of claim 1, wherein:
the plurality of first image features comprises a pseudo-image of the array.

12. The user interface of claim 1, wherein the plurality of data features each represent a quantification of degree, efficiency, or intensity of hybridization of a 20 probe based on the probe hybridizing with none, one or a plurality of targets.

13. The user interface of claim 12, wherein the second openable window comprises a two-dimensional scatter plot wherein the plurality of data features comprises marks on the scanner plot, each representing a quantification of degree, 25 efficiency, or intensity of hybridization of a probe with first and second targets.

14. The user interface of claim 12, wherein the second openable window comprises a histogram wherein the plurality of data features comprises bars, each representing a quantification of a number of probes having in common a range of 30 degree, efficiency, or intensity of hybridization with one or more targets.

15. The user interface of claim 12, wherein the second openable window comprises a graphical representation selected from the group consisting of a scatter plot, histogram, bar graph, or line graph.

5

16. The user interface of claim 1, wherein the plurality of descriptive features comprises rows of a spreadsheet wherein each row includes one or more descriptive elements associated with a probe.

10

17. The user interface of claim 1, wherein the descriptive elements comprise any one or more of the group of elements consisting of absolute image intensity value, relative image intensity value, user-supplied data related to the probe, biological information related to the probe; probe identifier, probe x-coordinate identifier, probe y-coordinate identifier, probe-related data, probe data links, pin identifier, well plate identifier.

15

18. The user interface of claim 17, wherein the probe data links include links to remotely or locally stored user-supplied data related to the probe or links to remotely or locally stored biological information related to the probe.

20

19. The user interface of claim 17, wherein the probe-related data include any one or more datum selected from the group consisting of chromosome location of a gene or EST represented by the probe, band location on the chromosome, or SNP or other marker identifying the location on the chromosome.

25

20. The user interface of claim 1, wherein when a user selects a first image feature associated with a first probe, a data feature or a descriptive feature associated with the first probe, or both, are highlighted.

21. The user interface of claim 1, wherein when a user selects a data feature associated with a first probe, a first image feature or a descriptive feature associated with the first probe, or both, are highlighted.

5 22. The user interface of claim 1, wherein:
when a user selects a descriptive feature associated with a first probe, a first image feature or a data feature associated with the first probe, or both, are highlighted.

10 23. A user interface, comprising:
two or more windows selected from the group consisting of
a first window having a plurality of image features, each having one or more characteristics representing one or more hybridization reactions associated with a probe of a probe array;
a second window having a plurality of data features, each relating to
15 one or more quantifications of one or more hybridization reactions associated with a probe of the probe array; and
a third window having a plurality of descriptive features, each including one or more descriptive elements associated with a probe of the probe array;
wherein, when a user selects a feature from any of the two or more windows, a
20 corresponding feature in at least one other of the two or more windows is highlighted.

24. A computer program product comprising:
(a) an image processor constructed and arranged to process image data based on scanning a probe array; and
25 (b) a GUI manager constructed and arranged to provide two or more windows selected from the group consisting of
(i) a first window having a plurality of image features based on the processed image data, each having one or more characteristics representing one or more hybridization reactions associated with a probe of the probe array,

(ii) a second window having a plurality of data features, each relating to one or more quantifications of one or more hybridization reactions associated with a probe of the probe array, and

- (iii) a third window having a plurality of descriptive features, each including one or more descriptive elements associated with a probe of the probe array.

25. The computer program product of claim 24, wherein:
when a user selects a feature from any of the two or more windows, the GUI manager further is constructed and arranged to cause a corresponding feature in at least one other of the two or more windows to be highlighted.

26. The computer program product of claim 24, wherein the probe array is a spotted array.

15 27. The computer program product of claim 24, wherein the probe array is a synthesized array.

28. A computer program product comprising:
a GUI manager constructed and arranged to provide two or more windows
20 selected from the group consisting of
(i) a first window having a plurality of image features, each having one or more characteristics representing one or more hybridization reactions associated with a probe of a probe array,
(ii) a second window having a plurality of data features, each relating to one or more quantifications of one or more hybridization reactions associated with a probe of the probe array, and
25 (iii) a third window having a plurality of descriptive features, each including one or more descriptive elements associated with a probe of the probe array.

30 29. A method comprising the steps of:
(a) providing image data based on scanning a probe array; and

- (b) providing in a graphical user interface two or more windows selected from the group consisting of
- (i) a first window having a plurality of image features based on the image data, each having one or more characteristics representing one or more hybridization reactions associated with a probe of a probe array,
 - 5 (ii) a second window having a plurality of data features, each relating to one or more quantifications of one or more hybridization reactions associated with a probe of the probe array, and
 - (iii) a third window having a plurality of descriptive features, each
- 10 including one or more descriptive elements associated with a probe of the probe array.

30. The method of claim 29, further comprising the steps of:
- (c) receiving a user selection of a feature from any of the two or more windows; and
 - 15 (d) causing a corresponding feature in at least one other of the two or more windows to be highlighted.

31. A scanning system, comprising:
- (a) a scanner constructed and arranged to scan a probe array to generate image data;
 - 20 (b) an image processor constructed and arranged to process the image data; and
 - (c) a GUI manager constructed and arranged to provide two or more windows selected from the group consisting of
- 25 (i) a first window having a plurality of image features based on the processed image data, each having one or more characteristics representing one or more hybridization reactions associated with a probe of the probe array,
- (ii) a second window having a plurality of data features, each relating to one or more quantifications of one or more hybridization reactions associated with
- 30 a probe of the probe array, and

(iii) a third window having a plurality of descriptive features, each including one or more descriptive elements associated with a probe of the probe array.

32. A scanning system, comprising:

5 a scanner constructed and arranged to scan a probe array to generate image data;

a computer; and

a computer program product that, when executed on the computer, performs a method comprising the steps of:

10 (a) processing the image data, and

(b) providing in a graphical user interface two or more windows

selected from the group consisting of

15 (i) a first window having a plurality of image features based on the processed image data, each having one or more characteristics representing one or more hybridization reactions associated with a probe of a probe array,

(ii) a second window having a plurality of data features, each relating to one or more quantifications of one or more hybridization reactions associated with a probe of the probe array, and

20 (iii) a third window having a plurality of descriptive features, each including one or more descriptive elements associated with a probe of the probe array.

33. The method of claim 32, wherein:

25 the method performed by the computer program product further includes the steps of

(c) receiving a user selection of a feature from any of the two or more windows, and

(d) causing a corresponding feature in at least one other of the two or more windows to be highlighted.

34. A computer system for providing a user interface with a scanner for scanning a probe array to generate image data, comprising:

a first window means for providing image feature means having one or more characteristics representing one or more hybridization reactions associated with probe means of the probe array;

a second window means for providing a data feature means related to one or more quantification means of one or more hybridization reactions associated with probe means of the probe array; and

a third window means for providing descriptive feature means including one or more descriptive elements associated with probe means of the probe array.

35. A computer system for providing a user interface with a scanner for scanning a probe array, the system being programmed to display image features having one or more characteristics representing one or more hybridization reactions associated with a probe of the probe array, data features related to one or more quantifications of one or more hybridization reactions associated with a probe of the probe array, and descriptive features including one or more descriptive elements associated with a probe of the probe array.

36. A computer program product comprising a GUI manager constructed and arranged to provide display regions for displaying image features representing hybridization associated with a probe of a probe array, data features related to quantifying the hybridization associated with a probe of the probe array, and descriptive features associated with a probe of the probe array.

25

37. A computer program product comprising a GUI manager means for providing window means for displaying image feature means representing hybridization means associated with a probe means of a probe array, data feature means related to quantifying hybridization means associated with probe means of the probe array, and descriptive feature means associated with probe means of the probe array.

FIGURE 1

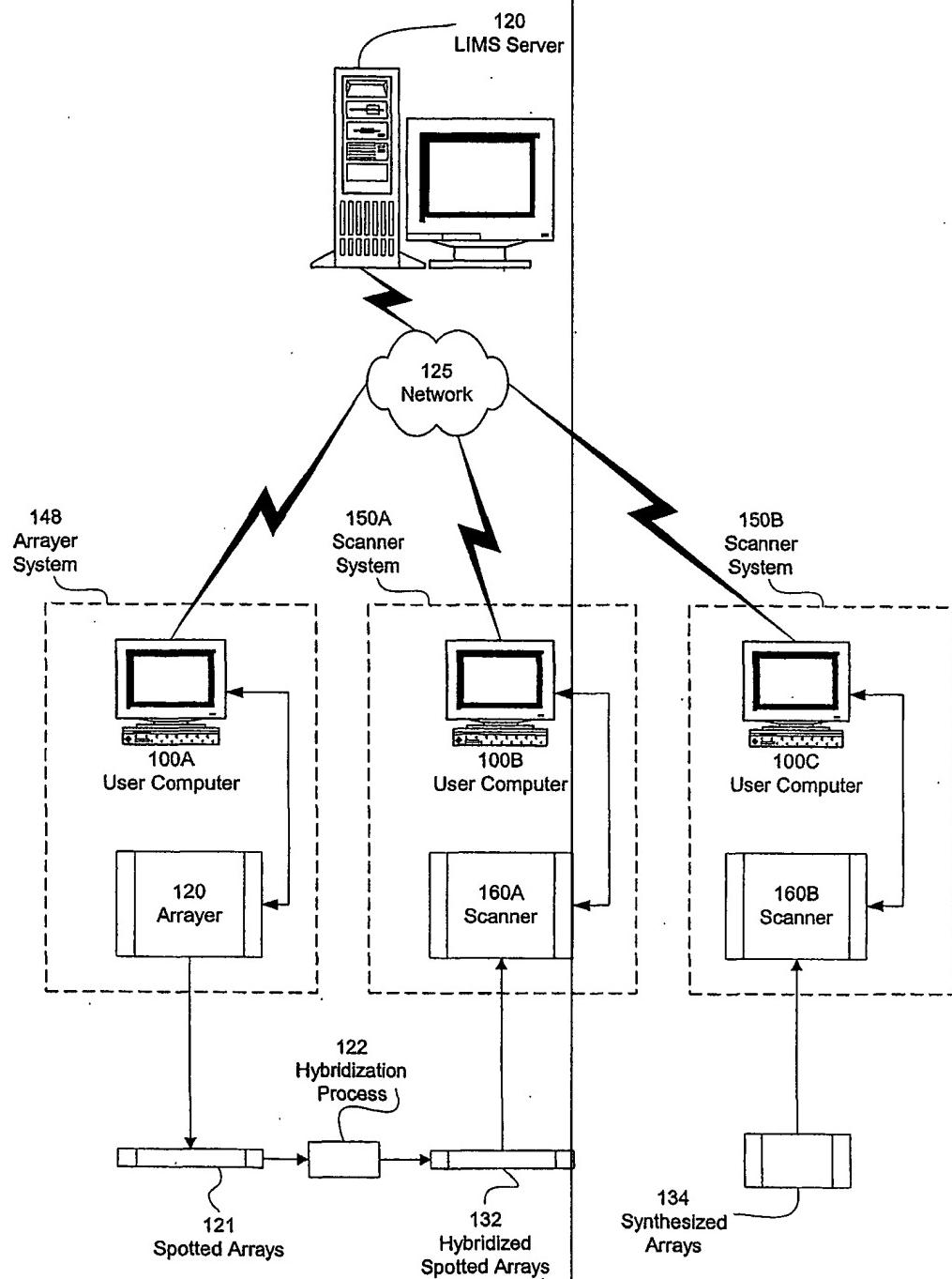
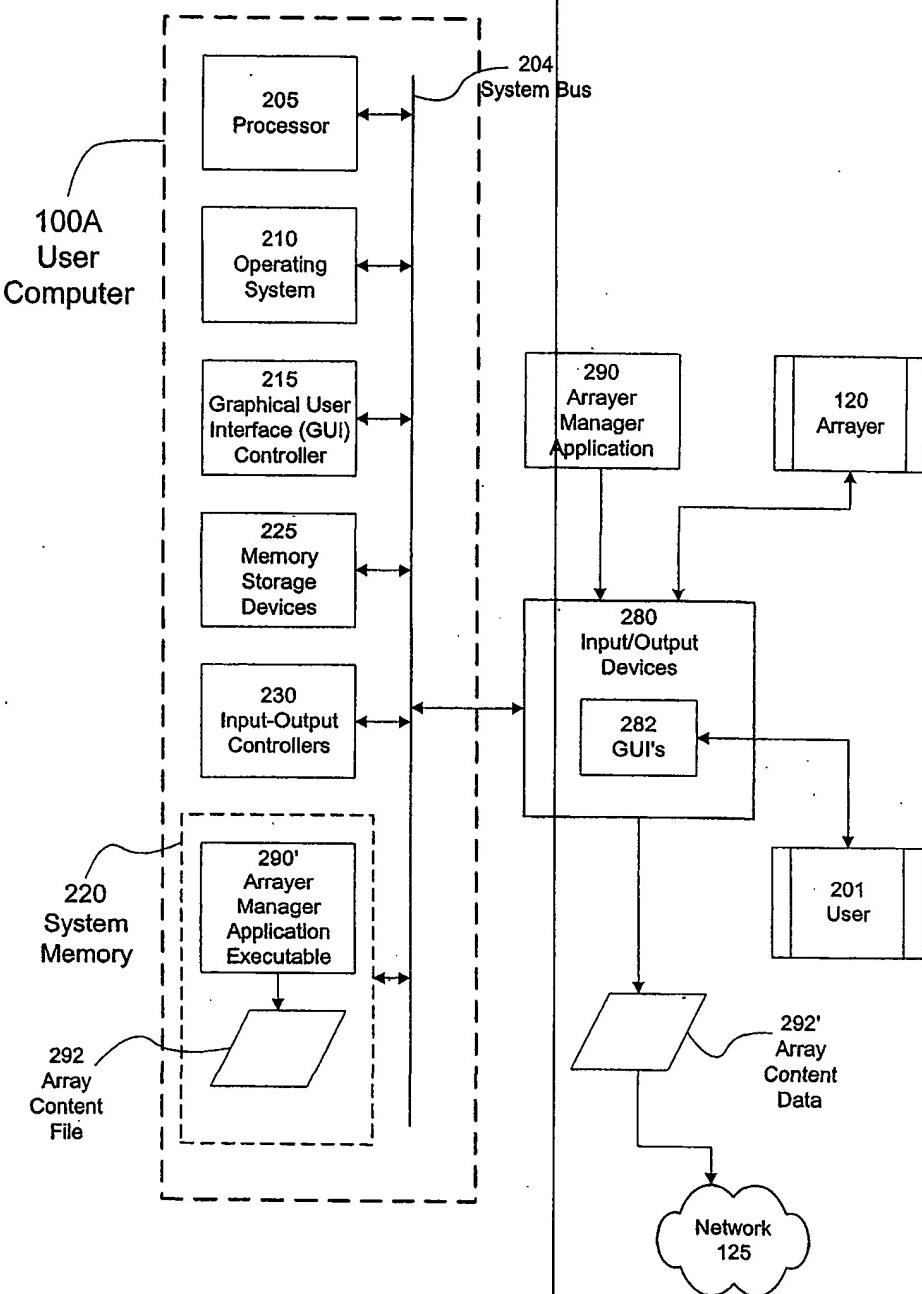
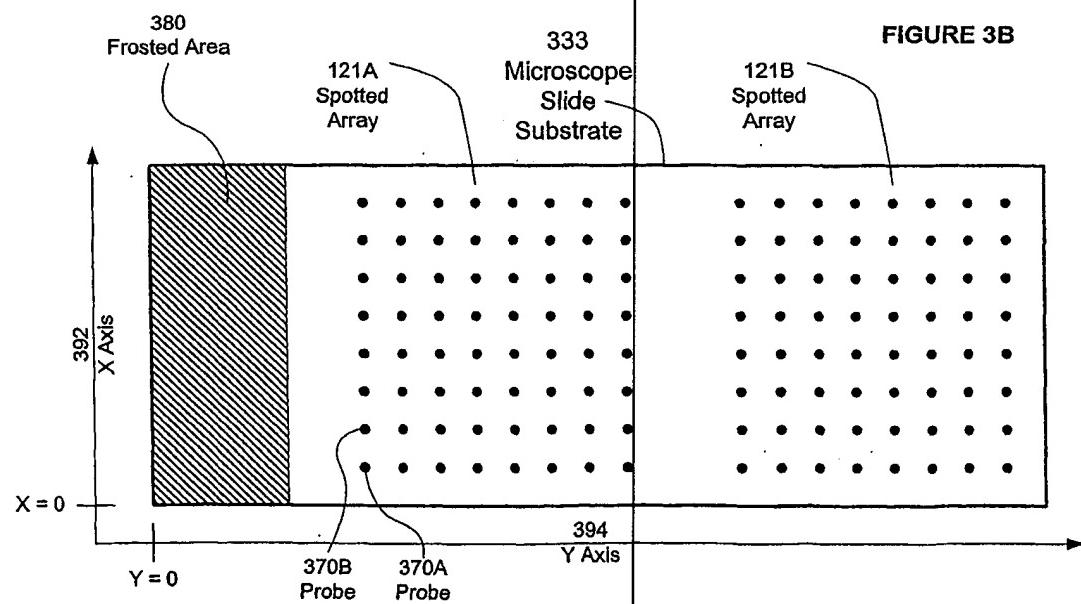
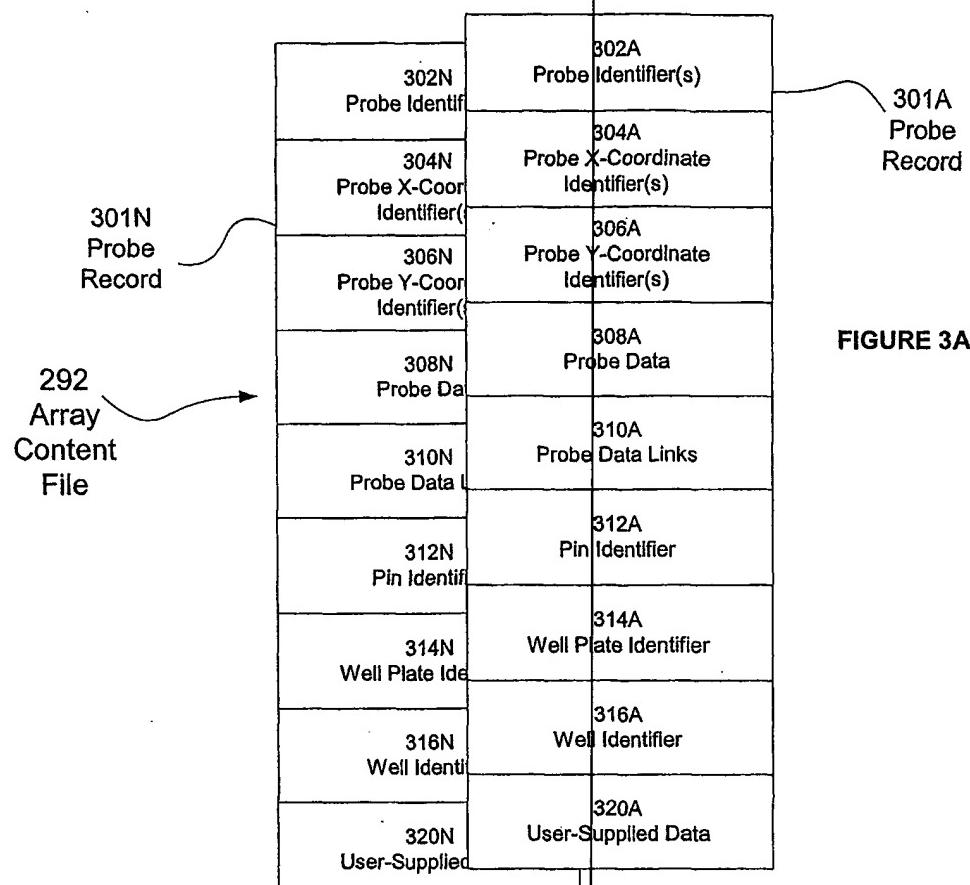


FIGURE 2





400 SCANNER OPTICS AND DETECTORS

FIGURE 4.

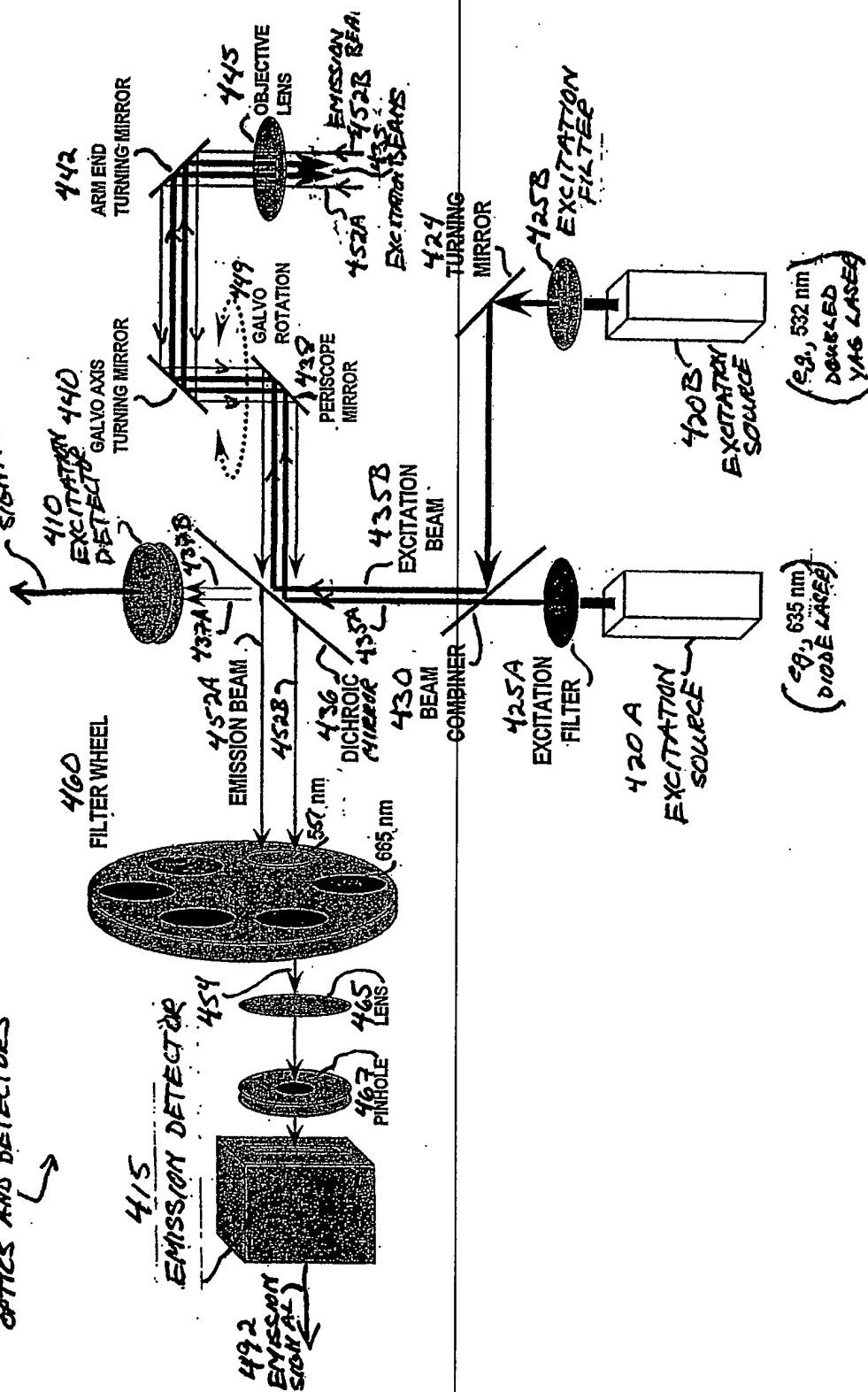


FIGURE 5A

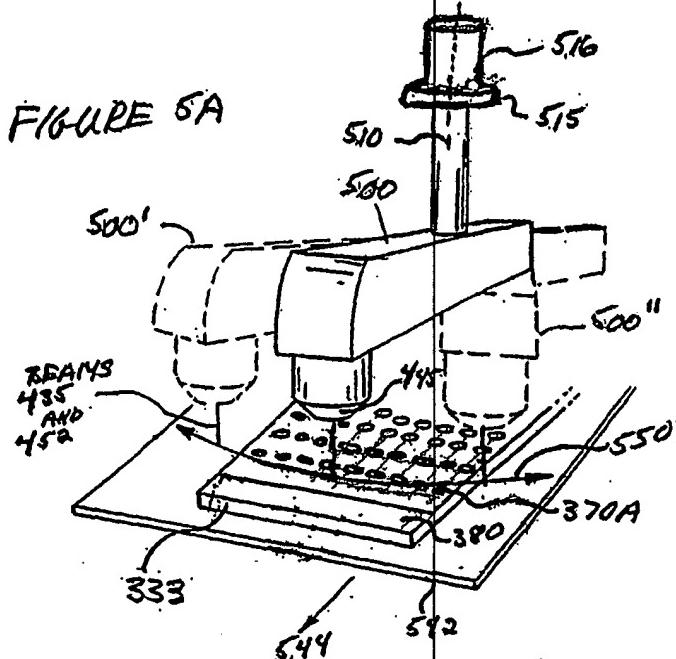
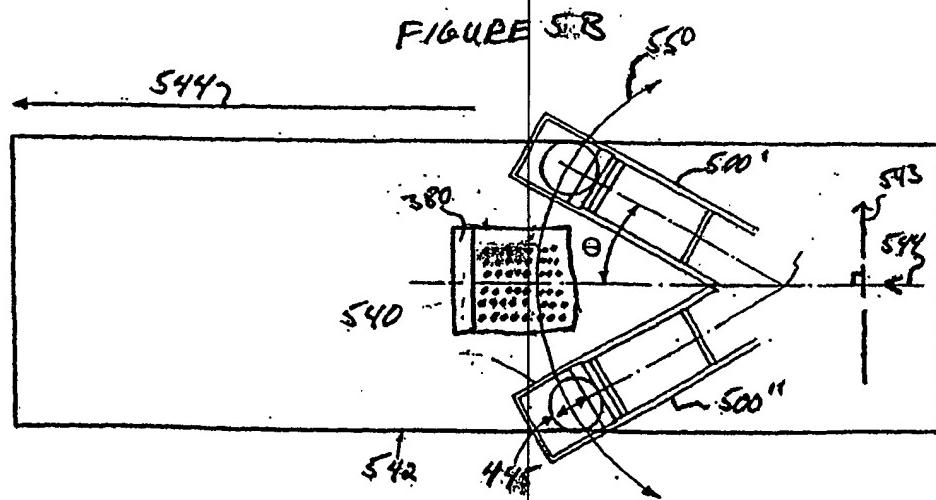
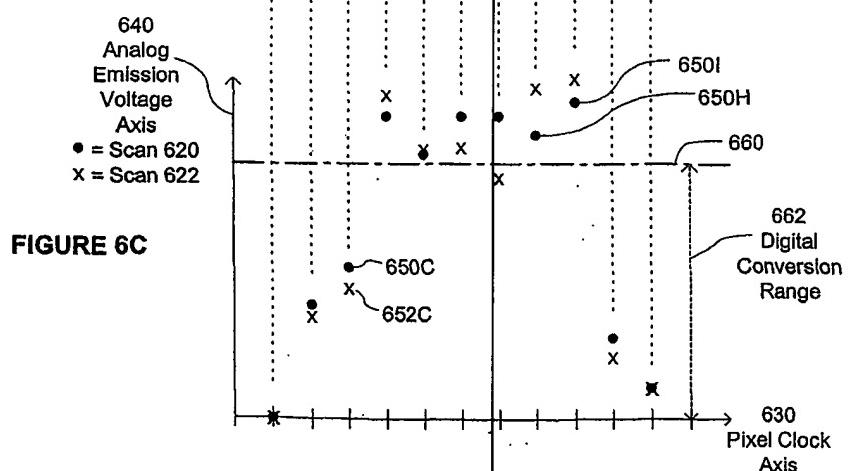
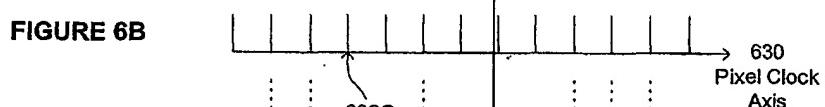
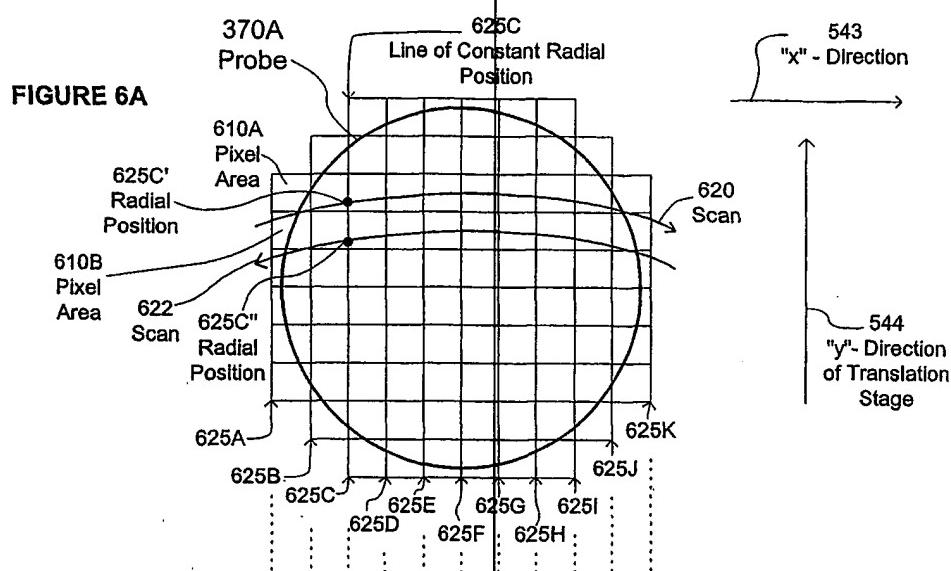


FIGURE 5B 550





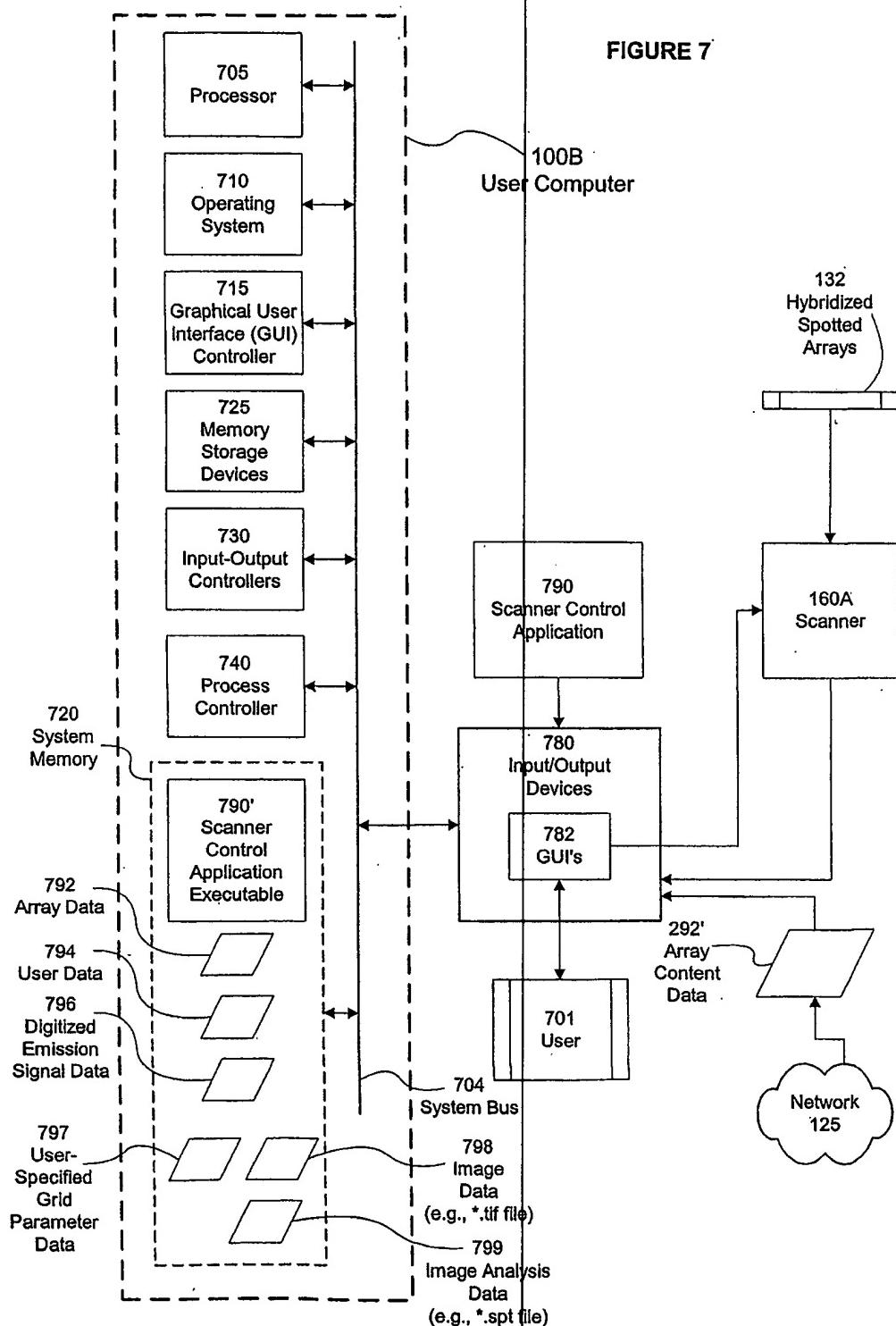
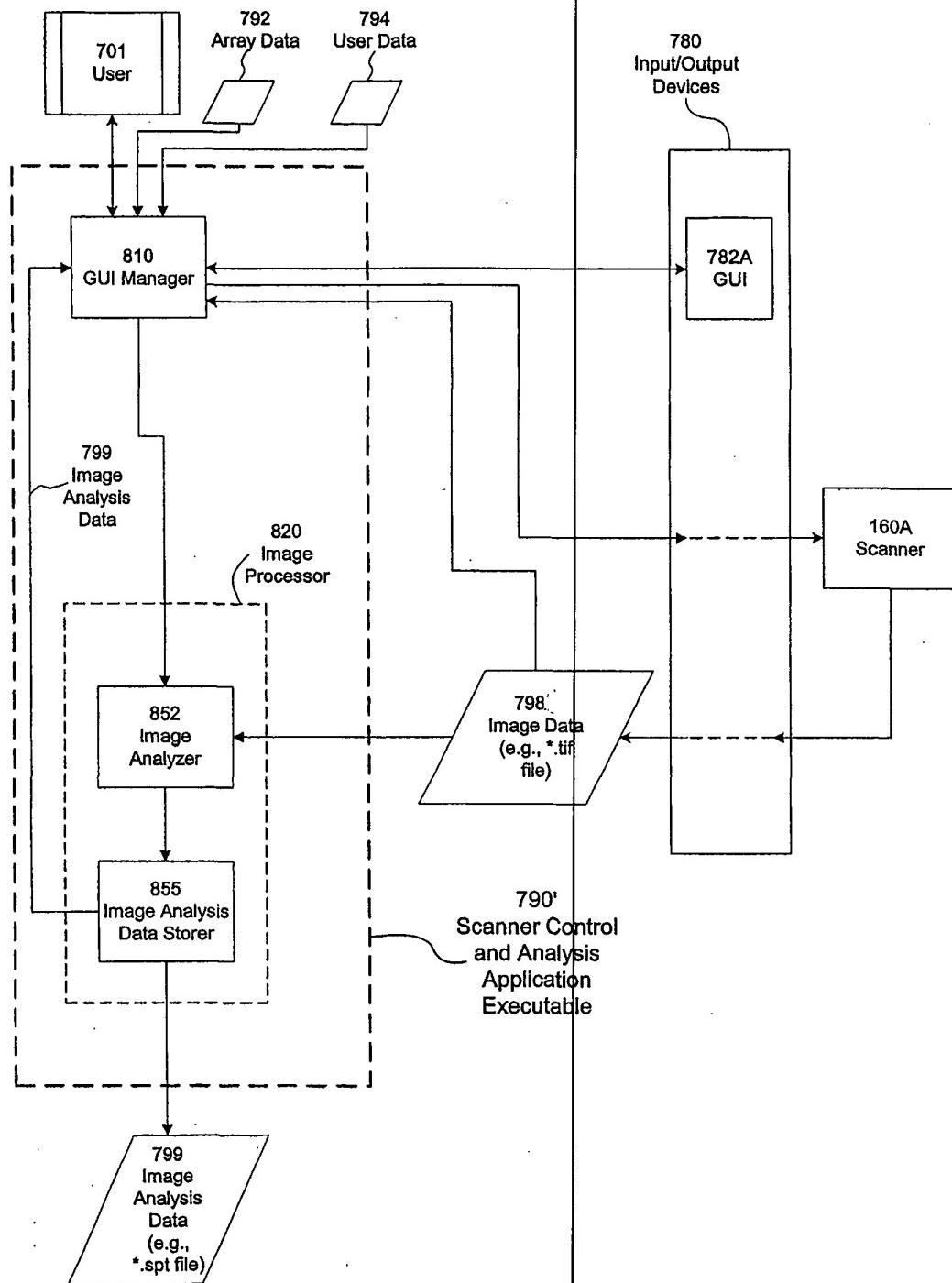
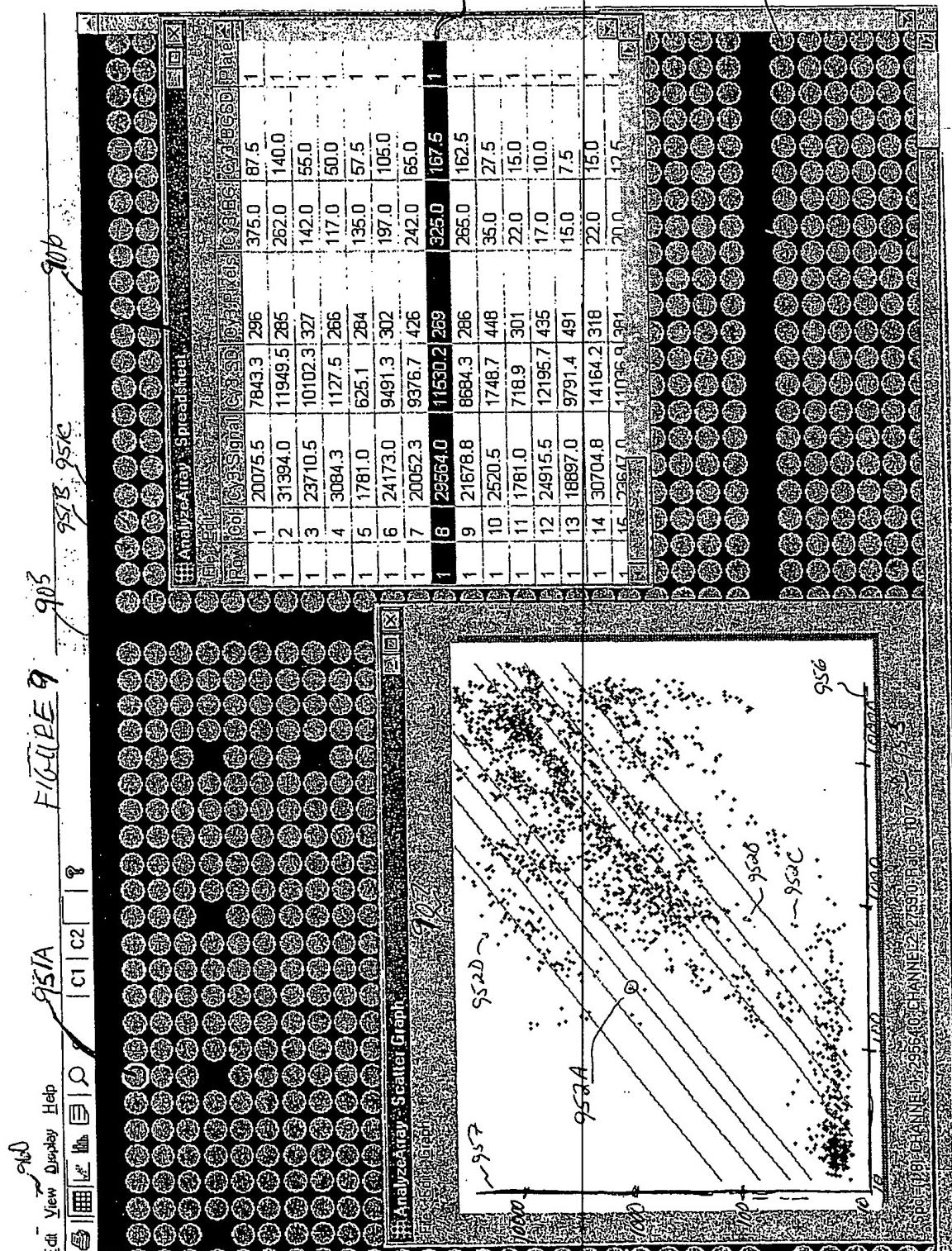


FIGURE 8





(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
10 May 2002 (10.05.2002)

PCT

(10) International Publication Number
WO 02/037209 A3

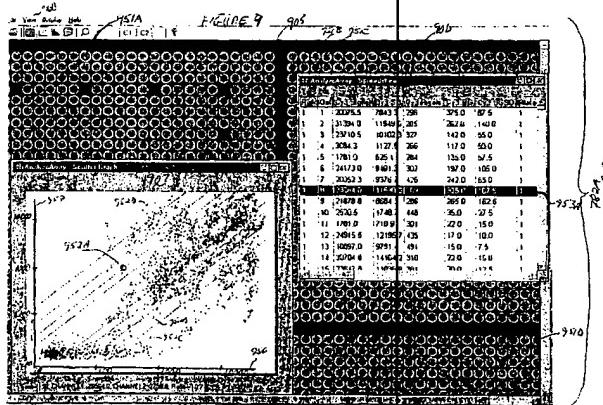
(51) International Patent Classification ⁷ :	G06F 3/14	CA 95135 (US). JEVONS, Luis [US/US]; 701 Ramona Avenue, Sunnyvale, CA 95135 (US).
(21) International Application Number:	PCT/US01/26390	
(22) International Filing Date:	22 August 2001 (22.08.2001)	(74) Agent: ZITKOVSKY, Ivan, D.; 6 Freeman Circle, Lexington, MA 02421-7713 (US).
(25) Filing Language:	English	(81) Designated States (<i>national</i>): CA, JP, US.
(26) Publication Language:	English	(84) Designated States (<i>regional</i>): European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR).
(30) Priority Data:		Published: — with international search report
60/226,999	22 August 2000 (22.08.2000)	US
60/286,578	26 April 2001 (26.04.2001)	US
(71) Applicant (for all designated States except US): AFFYMETRIX, INC [US/US]; 3380 Central Expressway, Santa Clara, CA 95051 (US).		(88) Date of publication of the international search report: 29 August 2002

(72) Inventors; and

(75) Inventors/Applicants (for US only): KAUSHIKKAR, Shantanu, V. [IN/US]; 3343 Ariel Joshua Court, San Jose,

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: SYSTEM, METHOD, AND COMPUTER SOFTWARE PRODUCT FOR LINKED WINDOW INTERFACES



(57) Abstract: Systems, methods, and computer program products are described for providing a graphical user interface (GUI, 782A) that may include a first openable window (905) of image features constituting, for example, a pseudo-image of a scanned probe array. The image features each have one or more characteristics representing one or more hybridization reactions associated with a probe of the probe array. The GUI also has a second openable window including data features, each relating to one or more quantifications of one or more hybridization reactions associated with a probe of the probe array. This second window (906) may be, for example, a scatter plot of hybridization intensities of probes to two or more labeled samples. The GUI further includes a third openable window (907) including descriptive features such as rows of a spreadsheet. Each row may include descriptive elements associated with a probe. When a user selects a feature from any of the two or more windows, a corresponding feature in at least one other of the two or more windows is highlighted.

WO 02/037209 A3

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US01/26390

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) :G06F 9/14

US CL :Please See Extra Sheet.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 345/771,804,805,895,853,810,965,781,841,440; 707/503; 700/266,268; 702/22,23,27,28

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

WEST, IMAGES SEARCH

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5,939,719 A (PARK ET AL) 17 AUGUST 1999, SUMMARY, FIGURE 13	1-37
A	US 5,714,756 A (PARK ET AL) 03 FEBRUARY 1998, ABSTRACT, SUMMARY, FIGURE 13	1-37
A,P	US 6,323,852 B1 (BLOWER Jr. ET AL) 27 NOVEMBER 2001, SUMMARY, FIGURE 2	1-37
A,P	US 6,236,456 B1 (GIEBELER ET AL) ABSTRACT, SUMMARY	22 MAY 2001, 1-37

<input type="checkbox"/>	Further documents are listed in the continuation of Box C.	<input type="checkbox"/>	See patent family annex.
"A"	Special categories of cited documents: document defining the general state of the art which is not considered to be of particular relevance	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"E"	earlier document published on or after the international filing date	"X"	document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Y"	document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"O"	document referring to an oral disclosure, use, exhibition or other means	"&"	document member of the same patent family
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 08 MAY 2002	Date of mailing of the international search report 31 MAY 2002
--	---

Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-9290	Authorized officer THOMAS T. NGUYEN Telephone No. 703-308-7240
---	--

**This Page is Inserted by IFW Indexing and Scanning
Operations and is not part of the Official Record**

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- BLACK BORDERS**
- IMAGE CUT OFF AT TOP, BOTTOM OR SIDES**
- FADED TEXT OR DRAWING**
- BLURRED OR ILLEGIBLE TEXT OR DRAWING**
- SKEWED/SLANTED IMAGES**
- COLOR OR BLACK AND WHITE PHOTOGRAPHS**
- GRAY SCALE DOCUMENTS**
- LINES OR MARKS ON ORIGINAL DOCUMENT**
- REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY**
- OTHER:** _____

IMAGES ARE BEST AVAILABLE COPY.

As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.